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van Veen, Teelkien

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# CEREBRAL HEMODYNAMICS IN NORMAL AND COMPLICATED PREGNANCY

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# CHAPTER 1

## GENERAL INTRODUCTION

## 1.1 Introduction

During pregnancy, approximately 6-25% of women are diagnosed with some form of hypertension.[1-6] Although appropriate prenatal care has reduced the number of poor outcomes, hypertensive disorders of pregnancy are still among the leading causes of maternal mortality and severe morbidity in both developed[6-8] and developing countries,[9, 10] accounting for more than 50,000 maternal deaths annually.[3] While the absolute mortality is much lower in developed countries, hypertension has nevertheless been implicated in approximately 20% of maternal deaths,[8, 9, 11] with cerebrovascular complications being the primary cause in over 50%.[7, 11, 12] Both the incidence of hypertension and the morbidity/mortality rate are affected by geographic, social, economic, and racial differences,[11, 13, 14] with the incidence of the latter two rising.[15, 16] This trend is thought to be caused by changes in maternal characteristics, such as increasing number of mothers with advanced maternal age, presence of comorbidities and higher pre-pregnancy weight.[3] Although rare, eclampsia, the onset of seizures or coma in a preeclamptic woman, is still the most feared pregnancy complication, with a mortality rate of approximately 1% in developed countries,[7, 17-19] but as high as 26% in developing countries.[20-22]

## 1.2 Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy range in a spectrum from chronic hypertension (CHTN) to gestational hypertension (GHTN), preeclampsia (PE), and superimposed preeclampsia in the setting of chronic hypertension (SiPE).[23] All are part of a dynamic process, where CHTN can progress to SiPE, and GHTN to PE and patients can deteriorate rapidly.[23]

Hypertension itself is defined as a systolic blood pressure (BP) of 140 mmHg or greater, a diastolic blood pressure of 90 mmHg or greater, or both, documented on at least two occasions, at least 4–6 hours apart.[13] In case of a BP ≥ 160 mmHg systolic and/or ≥ 110 mmHg diastolic, hypertension is confirmed within a short interval.[23]

Proteinuria is defined as ≥ 300 mg per 24-hour urine collection, protein/creatinine ratio ≥ 0.3, or 1+ dipstick reading if other methods are not available.[23]

*Preeclampsia* (PE) is a systemic disorder that is typically characterized by new-onset hypertension and proteinuria in pregnancy after the 20th week of pregnancy in a previously normotensive woman. In the absence of proteinuria, PE is diagnosed as hypertension with new development of thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbances.[23]

Despite being the focus of many studies, the exact pathophysiology of preeclampsia remains unclear. The leading hypotheses are based on disturbed placental function in early pregnancy leading to placental under perfusion, and possibly hypoxia and ischemia, followed by release of components from the intervillous space into the maternal circulation, causing an angiogenic imbalance and an enhanced maternal intravascular systemic inflammatory response. This leads to generalized maternal endothelial dysfunction and, hence, symptomatic clinical disease, by which the fetus, central nervous system, lungs, liver, kidneys, systemic vasculature, coagulation, and the heart may be affected.[1] Involvement of the brain can cause eclampsia: grand mal seizures or coma in a woman with preeclampsia, in the absence of other neurologic conditions that could account for the seizure.[13]

Risk factors for the development of PE are advanced maternal age, nulliparity, history of preeclampsia, and multifetal gestations.[1, 24] Preexisting medical conditions such as chronic hypertension, diabetes, obesity, renal disease and chronic autoimmune diseases also increase the risk for PE.[1, 24] The precise mechanism of these risk factors are not fully understood, but several factors are related to underlying maternal endothelial dysfunction, which may increase susceptibility of the vasculature to the effects of circulating factors.[25] This theory is supported by the fact that patients with chronic hypertension, diabetes, proteinuria or obesity develop PE at a lower level of angiogenic disturbance,[26, 27] Nulliparity and multifetal gestations, which are also associated with increased preeclampsia risk, have a slight disturbance even without having PE.[25]

*Gestational hypertension* (GHTN) is defined as hypertension that develops in pregnancy after 20 weeks gestation and which returns to normal within 12 weeks postpartum. Proteinuria or systemic

symptoms as seen in preeclampsia are absent.[23] GHTN is the most frequent cause of hypertension during pregnancy, affecting 6-17% of healthy nulliparous women.[5, 28] Preeclampsia may be subsequently diagnosed if proteinuria or other sign of preeclampsia develop. This occurs in 26-46%,[29, 30] and the likelihood of progression increases with earlier gestational age at presentation.[29, 30]

Maternal risks and incidence of adverse outcomes associated with gestational hypertension are generally less than those with preeclampsia. However, severity of hypertension is an important predictor of risks, and women with severe gestational hypertension may be at higher risk of adverse maternal and perinatal outcomes than women with mild pre-eclampsia.[28]

*Chronic hypertension* (CHTN) in pregnancy is defined as hypertension present before pregnancy or before the 20$^{th}$ week of gestation. Hypertension first diagnosed after 20 weeks gestation, and persisting 12 weeks postpartum, is also considered chronic hypertension.[31] The incidence of chronic hypertension is rising, and currently affects 7.7% of the women in the reproductive age range in the United States.[32] Concurrently, the prevalence of pregnancies complicated by CHTN is increasing (from 1.01% in 1995-1996 to 1.76% in 2007-2008).[33]

CHTN is associated with increased rates of adverse maternal and fetal outcomes both acute and long term, including premature birth, fetal growth restriction, fetal demise, placental abruption, superimposed preeclampsia, pulmonary edema and cesarean delivery.[31, 33-35] These complications are related to the duration of the disease, severity of the hypertension, presence of end organ damage, comorbidities, and noncompliance with prenatal visits.[31, 33, 34]

*Preeclampsia superimposed upon chronic hypertension* (SiPE) is new onset proteinuria after 20 weeks of gestation in a woman with chronic hypertension. In case of baseline proteinuria, SiPE is defined by a sudden increase in proteinuria, worsening or resistant hypertension in the last half of pregnancy or development of signs and symptoms of severe preeclampsia.[31]

The risk for developing SiPE is increased in women with a

history of SiPE, raised body mass index, African-American ethnicity, who were diagnosed at least four years earlier and who had a booking diastolic blood pressure >100 mmHg.[24, 35, 36] The incidence of SiPE has been reported to be between 12 and 29% of women with CHTN,[35-38] and up to 52% in cases of severe chronic hypertension in the first trimester.[39] Differentiating SiPE from an exacerbation of chronic hypertension can be difficult.

## 1.3 Cerebrovascular complications of hypertension in pregnancy

While multiple maternal organs can be affected, cerebral involvement is one of the most feared complications as it can lead to death or significant schort- or long-term morbidity.[8, 11] The risk of cerebrovascular complications during pregnancy is increased in all hypertensive disorders,[32, 40-42] but is most pronounced in severe pre-eclampsia.[41, 42] The neurological complications range from headache, visual disturbances and hyperreflexia to tonic-clonic seizures, coma and cerebrovascular accidents. Gross and microscopic histopathology have demonstrated intracerebral hemorrhage, petechiae, cerebral edema, vasculopathy, ischemic brain damage, microinfarcts, and fibrinoid necrosis.[43, 44] Magnetic resonance imaging (MRI) has shown abnormal scans with non-specific foci of increased signal in the deep cerebral white matter on T2-weighted images in 50% of the women with severe pre-eclampsia.[45] Widespread diffuse cerebral edema or localized hypodense lesions have been found with computed tomography (CT) imaging. In the absence of serious neurological symptoms, imaging is predominantly unremarkable.[43]

The pathophysiology of these cerebrovascular complications remains poorly understood. Two opposing theories are both based on endothelial dysfunction, and poor cerebral autoregulation: the "vasoconstriction/hypoperfusion," and the "hypertension/hyperperfusion" theories.[46] The first theory suggests that endothelial dysfunction, caused by systemic toxicity, leads to vasoconstriction, ischemia, and subsequent brain edema due to increased permeability of endothelium.[46] This theory is supported by the vasospasm seen on cerebral angiograms in some women with eclampsia[47, 48] the fact that

vasogenic edema is typically found in the watershed zones[49] and the systemic vasoconstriction seen in preeclampsia.[1]

The second theory is based on loss of cerebral autoregulation. In the presence of endothelial dysfunction, sudden elevations in systemic blood pressure may exceed the cerebrovascular autoregulatory capacity, leading to forced dilatation of cerebral arteries, causing hyperperfusion, blood-brain barrier disruption and edema.[50-52] Interestingly, 20-40% of eclamptic patients never develop overt hypertension prior to convulsions or a stroke,[17, 19, 53] suggesting an important role for autoregulatory dysfunction in the underlying pathophysiology.

In 1996, Hinchey *et al*. described a series of patients with a variety of disorders, including eclampsia, who all had similar neurologic complications (headache, visual disturbances, altered mental status and seizures) and radiologic findings (cerebral edema, mainly posterior), and named this condition reversible posterior leukoencephalopathy syndrome.[54] Severe preeclampsia-eclampsia is considered to be a form of this syndrome, which has been renamed to posterior reversible encephalopathy syndrome' (PRES).[55]

It remains unclear why the parieto-occipital lobes are most often involved,[50, 52, 54, 56] but it is hypothesized that the decreased sympathetic innervation of the vertebrobasilar arteries, as compared to that of the internal carotid artery system, plays a role.[57] Although the exact role of the autonomic nervous system on the regulation of cerebral blood flow remains controversial,[58] recent studies do suggest an autonomic, mainly sympathetic, role in cerebral blood flow control,[59, 60] protecting the brain from autoregulation breakthrough and loss of integrity of the blood- brain barrier.[61, 62] The decreased sympathetic innervation in the vertrobrobasilar region may allow autoregulatory breakthrough at a lower pressure than in other more densely innervated areas during acute hypertension.[57, 63]

Long-term consequences of eclampsia and preterm preeclampsia (gestational age <37 weeks) include an increased prevalence of cerebral white matter lesions seen on MRI when compared to control patients who had either a normotensive pregnancy or a pregnancy complicated by term preeclampsia.[64, 65] However, these lesions are found equally in patients with and without seizures, and are mainly located in

the frontal areas of the brain[66] making a direct causal relationship between PRES and these white matter lesions unlikely. The finding does raise the possibility that formerly (pre)eclamptic women are predisposed to develop cerebrovascular disease in later life.[66]

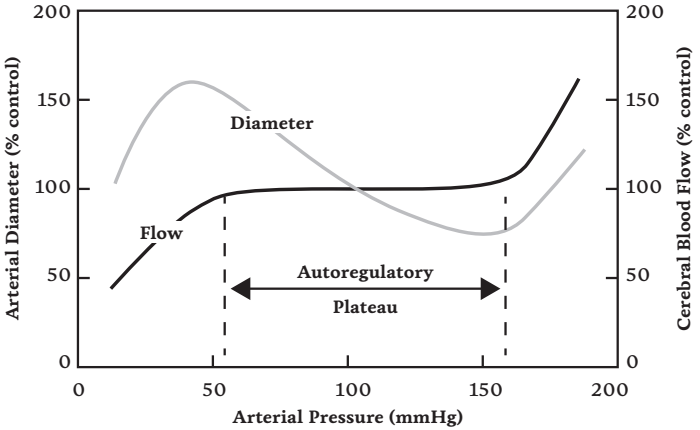


***Figure 1)*** *The cerebral autoregulation curve, adapted from Chillion and Baumbach 1997 and used with permission of Elsevier Limited for Academic Press.*[72]

## 1.4 Cerebral autoregulation

Under normal circumstances, cerebral blood flow is maintained at a relatively constant level, despite changes in blood pressure, through changes in the arterial diameter and hence cerebrovascular resistance (CVR). In 1959, Lassen introduced the term 'cerebral autoregulation' (CA) to describe this process.[67]

Measurement of the cerebral blood flow (CBF) was performed using indicator-dilution techniques, such as[133] Xenon or nitrous oxide, which required several minutes to obtain a single CBF value. This measurement was performed twice under steady state conditions: at a baseline blood pressure (BP), and after BP manipulation. The outcomes resulted in the classical CA curve, with a plateau between mean arterial pressures (MAP) of about 50-60 to 150-160 mmHg, where cerebral blood flow is kept constant in the case of normal autoregulation *(Figure 1)*.[68, 69] When the MAP exceeds this range, such

as in acute severe hypertension, autoregulation may be lost, and CBF increases linearly with increase in blood pressure.[68, 70] In this state of forced dilatation, the blood-brain barrier can be disrupted, leading to vasogenic (reversible) edema formation.[51, 71] Because the measurements used for this curve describe mean values of CBF and MAP averaged over several minutes, this concept is now known as static cerebral autoregulation.[69]

This paradigm, however, ignores the dynamic nature of autoregulation. Early animal studies, which used invasive testing for rapid measurement of CBF and BP, showed a characteristic transient CBF response to a sudden change in BP: after initially following BP, the CBF would return to its original baseline in a few seconds.[73, 74] In 1989, this same response was demonstrated in humans, using transcranial Doppler (TCD) and arterial volume clamping to obtain instantaneous values of CBFV and BP, while the BP alteration was induced by the release of thigh cuffs.[75] In addition to the efficiency of CA, which is evaluated by the static CA, this method also addresses the temporal course of CA, and is therefore named 'dynamic autoregulation'.[75] This thesis will predominantly focus on the dynamic autoregulation during pregnancy.

## 1.5 Cerebral autoregulation measurement

*Transcranial Doppler*

While ultrasound evaluation of extracranial vessels was first described in 1965,[76] the bony skull has long hindered the ultrasonic evaluation of the intracranial vasculature. However, Aaslid *et al*. showed in 1982 that low-frequency ultrasound (2-MHz pulsed Doppler) does penetrate the skull through certain natural cranial windows, where the cranial bone is relatively thin.[77] The transtemporal window, located above the zygomatic arch, is most often used for CA studies, because it allows for insonation of the main intracranial arteries. The middle cerebral artery (MCA), the largest and anatomical most ideally located,[77] is used in most CA studies.[78] A limitation of using TCD is that only the cerebral blood flow velocity (CBFV) can be obtained, and the method therefore relies on the assumption that changes in CBFV are directly proportional to changes in CBF, which

is only true if the vessel diameter is constant. Available literature shows that the MCA does not change in diameter despite significant changes in $PaCO_2$ or BP[79-81] and that it maintains its diameter during pregnancy.[82, 83] If this constant diameter is assumed, CBFV can be used as indicator for assessing CBF changes. The non-invasive nature and high temporal resolution make it possible to acquire the CBFV waveform and its transient changes in humans.[78]

*Non-invasive blood pressure measurement*

Because studies of CA evaluate the ability of the CBFV to return to baseline after a sudden change in BP, continuous recording of BP is required. While most critical care patients have an arterial line that can be used for this purpose, non-invasive techniques for the continuous measurement of BP are needed for research purposes including human subjects. The arterial volume clamping technique described by Peñaz, and converted by Wesseling into Finapres (Finger Arterial pressure), which measures the arterial pressure waveform at the finger, made this possible.[84] Comparison of estimates of CA derived from Finapres and from intra-aortic measurement demonstrated a good level of agreement between both methods.[85]

*Quantification of cerebral autoregulation*

In their initial study, Aaslid *et al*. used the rate of regulation (RoR), defined as $(\Delta CVR/\Delta T) / \Delta BP$, to quantify the autoregulation response. This indicates the slope of the CBFV return to its baseline ($\Delta CVR/\Delta T$) after a sudden BP drop ($\Delta BP$), and was shown to decrease with increasing levels of end-tidal $CO_2$ ($EtCO_2$).[75]

Tiecks *et al*. developed a more refined model using a second-order differential equation.[69] This autoregulation index (ARI) ranges from 0 (absence of autoregulation, CBFV passively follows ABP) to 9 (best measurable autoregulation, *(Figure 2)*. Each of its values corresponds to a step change in CBFV that is expected by the theoretical step change in BP, characterized by three parameters: the time constant (T), the damping factor (D), and the autoregulatory dynamic gain (K). The curve that best fits the measured CBFV response defines the corresponding value of ARI.[69]

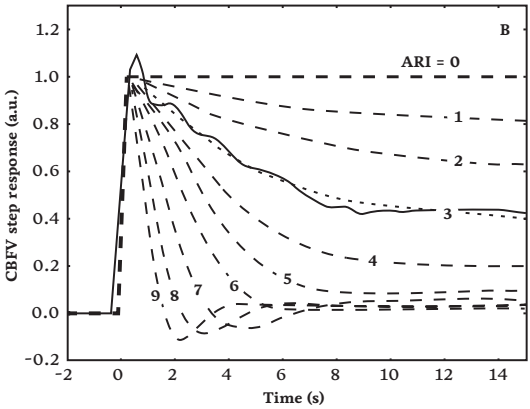


***Figure 2)*** *The 10 theoretical curves with associated ARI and an example of a measurement of which the best corresponding value was ARI = 3.*
*Used with permission from R.B. Panerai; Cerebral Autoregulation: From Models to Clinical Applications (2008)*[89]

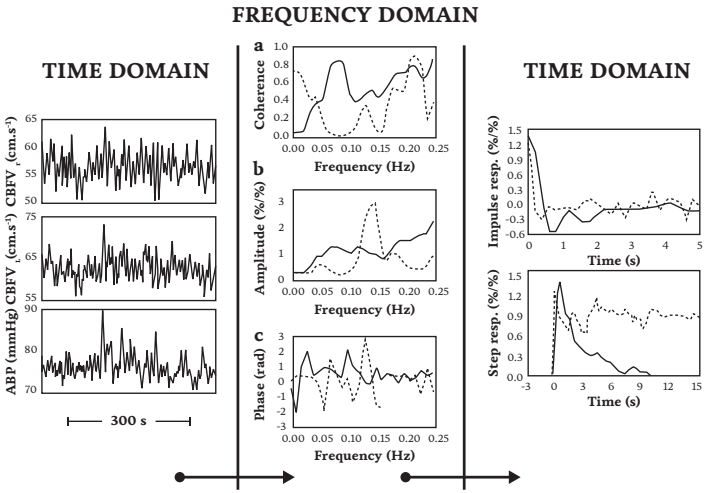


***Figure 3)*** *Parameters extracted by transfer function analysis from continuous blood pressure (ABP) and cerebral flood flow velocity (CBFV) measurements, converted into the frequency domain, and transformed back to the time domain to give an estimate of the impulse and step response. Indicating relatively normal (continuous line) and severely impaired (dashed line) autoregulation.*
*Used with permission from R.B. Panerai; Cerebral Autoregulation: From Models to Clinical Applications (2008)* [89]

To study CA, several maneuvers have been developed to induce the BP changes while measuring the CBFV response, including thigh cuff inflation, Valsalva maneuver, low frequency breathing, posture changes, lower-body negative pressure and pharmacological methods.[78] However, in some groups of participants, these interventions and a sudden drop in blood pressure might not be safe, and the procedures might not reflect a physiological situation. The method was therefore adapted to use spontaneous fluctuations of BP, after applying a fast Fourier transform algorithm to obtain the transfer function parameters coherence, gain and phase in the low frequency range of the frequency-domain.[86, 87] The inverse discrete Fourier transform of gain and phase transforms them back to the time-domain and gives an estimate of the CBFV impulse and step responses *(Figure 3)*. This method correlates well with the thigh cuff test[86] and is now a generally accepted method for the study of the dynamic cerebral autoregulation.[88]

The transfer function parameters coherence, gain and phase by themselves are also used as a measure of autoregulation.[87] Coherence, which is similar to a correlation coefficient, provides an indication of the correlation between the components at each frequency. A high coherence (approaching 1.0) would suggest that CBFV follows BP, and thus that the CA is impaired.[87] However, this can also result from low noise levels, and therefore gives information about the reliability of gain and phase estimates at each frequency.[78] Gain represents the degree to which the variables are amplified and is increased with worsening CA,[78] but is also affected by CBFV and critical closing pressure.[90] Phase indicates the time delay of the autoregulatory response, where a positive phase shift (indicating that CBFV changes before BP) indicates intact autoregulation. An inherent problem with phase is wrap-around, when absolute values of phase greater than $\pi$ radians are interpreted as being in the interval $\pm\pi$, confounding the analyses.[91] These three parameters combined indicate the extent to which the input signal, BP, is reflected in the output signal, CBF. While all three variables are needed to give a reliable estimate of cerebral autoregulation, several studies have based their conclusions on changes in only one of these.[89]

*Factors affecting dynamic cerebral autoregulation functionality*

The exact mechanisms of cerebral autoregulation remain unclear, but include metabolic, myogenic, and neurogenic regulation.[92] Metabolic regulation adjusts blood flow to metabolic demand, arterial tension of carbon dioxide ($PaCO_2$) and oxygen supply. The main physiological determinant of CA is $PaCO_2$. Hypercapnia causes vasodilation, increased CBF and CBFV and a decreased autoregulatory response, whereas hypocapnia has the reverse effect.[75, 90, 93] Activation of the brain increases the demand for oxygen and possibly weakens the CA function,[93-96] but mental activation is not controlled for in most studies.

Myogenic regulation indicates the effect of transmural blood pressure changes on vascular smooth muscle tension to keep blood flow constant. Under normal circumstances, brain vessels possess intrinsic vascular tone, and the cerebral arteries constrict in response to increased pressure, and dilate in response to decreased pressure. This is also known as the "Bayliss effect."[97]

While the cerebrovascular bed is well innervated by sympathetic nerve fibers,[57, 97] the exact role of the autonomic nervous system on the regulation of dynamic CA remains controversial.[58, 97] Sympathetic neurotransmitters have a significant vasoconstrictor effect,[57] but studies on their clinical function in static autoregulation are not consistent, except in the prevention of autoregulatory breakthrough and hyperperfusion during acute hypertension.[92] Recent work on dynamic CA suggests a role for the autonomic, and possibly primarily sympathetic, nervous system in the short term regulation of CA.[59, 60, 98]

Other factors affecting CA are body temperature, intracranial pressure, intra-thoracic pressure, and hematocrit.[94] Interestingly age does not seem to affect CA.[99] The effects of gender and hormonal changes, although less well studied, suggest that CA may be enhanced in women.[100]

Traumatic brain injury,[101] stroke,[102] carotid artery stenosis,[103] malignant hypertension[104] and neonatal prematurity[105] may all impair cerebral pressure autoregulation. These patients are at risk for secon-

dary brain injury from ischemia or vasogenic edema. Mild-to-moderate hypertension does not seem to affect the functionality,[106-108] while the effect of diabetes is conflicting, showing either impaired autoregulation[109, 110] or no difference.[111, 112]

*Other estimates of cerebrovascular hemodynamics*

The relationship between BP and CBFV can also be expressed by a single parameter the cerebrovascular resistance index:

$$CVRi = \frac{BP}{CBFV}$$

This formula assumes that the flow/velocity reaches zero when the perfusion pressure (BP) is also zero.[113] However, in many vascular beds, including the cerebral bed, flow/velocity can be zero at perfusion pressures greater than zero. This is known as the critical closing pressure (CrCP).[114] Direct measurement of CrCP in humans is not possible, but linear interpolation of the instantaneous relationship between CBFV and BP during each heart beat shows an interception of the pressure axis at values significantly greater than zero. The inverse of the regression slope represents the resistance-area product (RAP),[115] which has the same units as CVRi. *(Figure 4)*

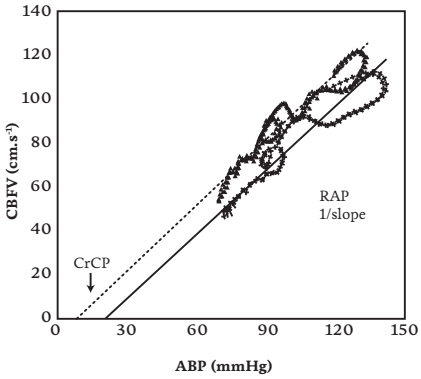


***Figure 4)*** *Representative instantaneous velocity–pressure relationship for one cardiac cycle and indicating the critical closing pressure (CrCP) and resistance area product (RAP) before (+) and during (Δ) 5% $CO_2$ breathing for one subject.*
*R.B. Panerai; Effect of $CO_2$ on dynamic cerebral autoregulation measurement (1999)[90]. Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing. All rights reserved*

These two parameters can be calculated as

$$CrCP = \frac{-a}{b} \text{ and } RAP = \frac{1}{b}$$

Therefore, CBFV can be expressed as

$$CBFV = \frac{BP\text{-}CrCP}{RAP}$$

Two other indices that often have been used to describe the cerebral hemodynamics in pregnancy are Pourcelot's resistance index (RI) and Gosling's pulsatility index (PI).[116]

$$RI = \frac{CBFV_{systolic} - CBFV_{diastolic}}{CBFV_{systolic}}$$

$$PI = \frac{CBFV_{systolic} - CBFV_{diastolic}}{CBFV_{mean}}$$

The relationship between PI and cerebrovascular resistance has been debated. While some see the PI as a good substitute for CVR,[117] the PI-CVR relationship may be disturbed by changes in upstream vascular resistance due to changes in the mechanoelastic properties of the large vessels.[118]

Lastly, a formula for the cerebral perfusion pressure (CPP) was adapted and validated in pregnancy by Belfort *et al*. to estimate the cerebral perfusion pressure (CPP).[119]

$$CPP = \frac{CBFV_{mean}}{CBFV_{mean} - CBFV_{diastolic}} X\ (BP_{mean} - BP_{diastolic})$$

*Subcomponent analysis*

Using a multivariate model of the CBFV, the independent contributions of BP, RAP, CrCP and CVR to changes in CBFV can be analyzed. Separating the different systemic and cerebral influences that account for the CBF response allows the identification of the different hemodynamic contributions to the CBFV response using standardized units of measurement of CBFV at any instant of time.

Therefore, the CBFV response can be broken down into subcomponents describing the relative contribution of each. The total percentage change in CBFV during breath holding can be represented in two ways: 1) as the sum of the simultaneous changes in BP, CrCP and RAP; and 2) as the sum of the changes in BP and CVRi.[113]

Using this method, it is suggested that CrCP is mainly influenced by the metabolic pathway, while RAP reflects myogenic activity in response to BP transients.[113]

These analyses might give more insight into the physiological interpretation of the cerebral hemodynamic anomalies seen in preeclampsia. This method is used in **Chapter 5** to compare the effect of breath holding between women with preeclampsia and a normotensive control group.

## 1.6 Cerebral hemodynamics in pregnancy and preeclampsia

*Cerebral hemodynamics in pregnancy*

The changes in central hemodynamics during pregnancy have been quite extensively studied and characterized, with both noninvasive[120] and invasive techniques.[121] The systemic cardiovascular changes are characterized by a large increase in cardiac output and plasma volume that is associated with a drop in systemic vascular resistance. The cerebral circulation is dependent on a constant blood supply, and relative intolerant to increases or decreases in blood volume. Our understanding of the adaptation of the cerebral circulation to these systemic hemodynamic changes is limited, because studies on cerebral hemodynamics and cerebrovascular structure are difficult to perform. Various imaging techniques have been applied to study the changes in maternal cerebral blood flow and animal models have been used to study the structural changes in the cerebral vasculature.

Several cross-sectional[122, 123] and longitudinal studies[82, 116, 124-127] have examined maternal cerebral blood flow during pregnancy, using various techniques (Doppler ultrasound and MRI) and studying various blood vessels (middle cerebral, posterior cerebral and carotid artery). The flow velocity[116, 124, 125] or flow volume and RI/PI in the middle cerebral artery (MCA) seems to be decreased in late-pregnancy when compared to non-pregnant women, while the CPP is

increased.[116] Nevo *et al*. showed an increase in the global CBF.[122]

Very few investigators have studied the other major intracranial arteries (anterior and posterior cerebral arteries).[82] This is most likely due to the greater difficulty in obtaining reliable Doppler signals from these vessels. In **Chapter 2,** the changes in cerebral blood flow velocity in the maternal anterior and posterior cerebral arteries during normal pregnancy and in the postpartum period are evaluated and compared to known values in the middle cerebral artery.

The exact mechanism of the changes in hemodynamics is not known, but might be caused by a combination of changes in carbon dioxide, hormones, cytokines, other circulating factors, and in perivascular innervation.[63, 128] The increased levels of female sex hormones in pregnancy cause respiratory alkalosis and hypocapnia.[129] This effect is almost fully established by 7-8 weeks of gestation.[129] $PaCO_2$ is one of the main physiological determinants of the cerebral blood flow: a decrease in $PaCO_2$ increases the cerebrovascular resistance, decreases cerebral blood flow velocity due to constriction of the small arteries, and improves the cerebral autoregulation,[93, 130, 131] Indeed, Brackley *et al*. showed an increase in RI by 4-7 weeks of gestation, compared with pre-pregnancy values, suggesting increased downstream resistance.[127] Estrogens have a direct vasodilator effect on the microvasculature[132] through endothelial nitric oxide synthase.[133]

The changes in cerebral autoregulation during pregnancy have not been studied in humans. In rats, the upper limit of autoregulation of the anterior and posterior circulations is slightly shifted to a higher pressure in late pregnancy, while the lower limit is shifted to the left only in the posterior artery when compared to non-pregnant rats.[63] However, only late-pregnant rats had significant cerebral edema in response to acute hypertension, suggesting that the blood-brain barrier is more vulnerable to disruption during pregnancy.[63] The effect of gestational age on autoregulation functionality in normal pregnancies is studied and compared to non-pregnant controls in **Chapter 3**.

While it is known that maternal demographic parameters such as age, race, pre-gestational hypertension, diabetes and obesity increase the risk for preeclampsia,[1, 24] their effect on the cerebral blood flow in pregnancy has only sparsely been studied. Pregnant

women with mild chronic hypertension have normal cerebral hemodynamics,[134] but those with gestational diabetes shown abnormal endothelium-dependent vasodilation after visual stimulation.[135] In **Chapters 6 and 7**, the consequence of hypertension, diabetes and obesity on the cerebral autoregulation in pregnancy is investigated.

*Cerebral hemodynamics in preeclampsia*

Several neuroradiological imaging techniques have been used to improve the understanding of cerebrovascular hemodynamic changes and the association with neurological symptoms seen in preeclampsia. Both TCD and MRI have shown increased cerebral blood flow velocity/volume in the MCA and PCA of women with preeclampsia when compared to normotensive controls,[49, 136-138] which persisted at least 48 hours postpartum,[139] but had returned to normal at 6 to 8 weeks after delivery.[136] Using TCD, the CPP variation in different hypertensive states of pregnancy has been studied. Belfort *et al*. showed that while preeclampsia can lead to either normal, under- or over-perfusion (as indicated by CPP and compared to 95% confidence intervals for normal pregnancy), 52% of women with mild preeclampsia have underperfusion and 59% of women with severe preeclampsia have overperfusion.[140] Furthermore, preeclamptic women with headache were much more likely to have abnormal CPP than those without headache,[141] and the CPP decreased after administration of labetalol[142] or magnesium sulfate.[143] Besides increased CPP and CBFV, multiple studies also reported decreased resistance[83, 137, 144, 145] and the severity of preeclampsia seems to correlate with the degree of any TCD abnormality.[83, 141, 144, 146]

The functionality of the cerebral vasculature has been studied by breath holding or breathing 5% $CO_2$. The hypercapnia that occurs as a result of these maneuvers leads to cerebral vasodilation and increased CBF, and reflects the ability of the vascular endothelium to adapt to changes in metabolic activity. This vasoreactivity is impaired in patients with conditions that have a predisposition for cerebrovascular disease, such as hypertension[147, 148] diabetes[147, 149] and carotid artery stenosis,[147, 150] and is thought to be the consequence of endothelial dysfunction.[147, 149] Previous studies in preeclampsia have shown conflicting results, with either impaired[145, 151] or unaffected[152]

vasoreactivity. However, none of these studies measured the CBF velocity (CBFV) or the blood pressure (BP) continuously, and therefore lack information on the temporal pattern of the physiologic changes associated with hypercapnia.

Little is known about the cerebral autoregulation in preeclampsia. Oehm *et al*. showed a reduced phase shift and elevated gain in three patients with preeclampsia or eclampsia who were being treated with magnesium sulfate, suggesting impaired autoregulation when compared with healthy pregnant controls.[153] Other studies interpreted increased CBFV, coupled with increased BP without increased resistance, as dysfunctional autoregulation.[144, 146, 154, 155]

In **Chapter 4**, the ARI is used to test the hypothesis that preeclampsia is associated with impaired dynamic cerebral autoregulation.

*Transcranial Doppler for prediction of preeclampsia*

While the development of the disorder or its progression cannot be prevented, identification of women at risk will aid in early diagnosis and appropriate management and may improve maternal and perinatal outcome.[1] Because the pathophysiological changes associated with preeclampsia begin early in pregnancy, many clinical, biochemical, and hematologic tests have been proposed as potential predictors for the future development of preeclampsia. For example, the maternal medical history, uterine artery Doppler,[156] systemic hemodynamics[157] and angiogenic balance[25] are different before the onset of preeclampsia compared with women whose gestations proceed normally. However, none are highly predictive.

The use of TCD for the prediction of preeclampsia is an attractive proposition given its non-invasive modality, relatively low cost and the ease of use. Results have however been conflicting. Riskin-Mashiah *et al*. showed that women destined to develop preeclampsia had lower resistance index (RI) and pulsatility index (PI) some weeks before the development of preeclampsia.[158] The same was true for women with chronic hypertension who subsequently developed SiPE when compared to those with CHTN who did not develop this.[159] However, Janzarik *et al*. did not find this association, with either the dynamic cerebral autoregulation parameters phase or gain.[160]

**Chapter 8** deals with the hypothesis that second trimester MCA Doppler RI values can be used to predict the subsequent development of preeclampsia. In **Chapter 6**, the ARI was used to compare those who did and did not develop PE later in their pregnancy.

## 1.7 Aims of the thesis

The aim of the research described in this thesis was to contribute towards a better understanding of maternal cerebral hemodynamics during normal pregnancy and in pregnancies complicated by hypertensive disorders, obesity and diabetes.

The following aims ware addressed:

*-To define the normal range of blood flow velocity and velocity ratios in the maternal anterior and posterior cerebral arteries during normal pregnancy and the postpartum period. (Chapter 2)*

*-To investigate the effect of gestational age on autoregulation functionality in normal pregnancy and to compare this to non-pregnant controls. (Chapter 3)*

*-To test the hypothesis that preeclampsia is associated with impaired dynamic cerebral autoregulation. (Chapter 4)*

*-To compare the cerebrovascular response to breath holding in women with preeclampsia and their normotensive counterparts by using subcomponent analysis (Chapter 5)*

*-To investigate the cerebral autoregulation in the hypertensive disorders of pregnancy (superimposed preeclampsia, preeclampsia, chronic hypertension and gestational hypertension), and to compare this with a control group consisting of normotensive pregnant women. (Chapter 6)*

*-To investigate the effect of pre-gestational diabetes type II, gestational diabetes and obesity on the cerebral autoregulation in pregnancy (Chapter 7)*

*-To investigate the use of transcranial Doppler derived resistance index and autoregulation index for the prediction of the development of subsequent preeclampsia (Chapters 6 and 8).*

## Abbreviations

| | |
|---|---|
| ARI: | *Autoregulation index* |
| BP: | *Blood pressure* |
| CA: | *Cerebral autoregulation* |
| CBF: | *Cerebral blood flow* |
| CBFV: | *Cerebral blood flow velocity* |
| CHTN: | *Chronic hypertension* |
| CPP: | *Cerebral perfusion pressure* |
| CrCP: | *Critical closing pressure* |
| CVR: | *Cerebrovascular resistance* |
| CVRi: | *Cerebrovascular resistance index* |
| $EtCO_2$: | *End-tidal carbon dioxide* |
| GHTN: | *Gestational hypertension* |
| MAP: | *Mean arterial pressure* |
| MCA: | *Middle cerebral artery* |
| $PaCO_2$: | *Arterial tension of carbon dioxide* |
| PE: | *Preeclampsia* |
| PI: | *Pulsatility index* |
| PRES: | *Posterior reversible encephalopathy syndrome* |
| RAP: | *Resistance area product* |
| RI: | *Resistance index* |
| SiPE: | *Superimposed preeclampsia* |
| TCD: | *Transcranial Doppler* |

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# CHAPTER 2

## GLOBAL CHANGES IN MATERNAL POSTERIOR AND ANTERIOR CEREBRAL ARTERY HEMODYNAMICS DURING PREGNANCY AND POSTPARTUM – A LONGITUDINAL STUDY

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## Abstract

***Purpose:*** *To longitudinally define the normal range of the blood velocity (and derived parameters) in the maternal anterior (ACA) and posterior cerebral arteries (PCA) during normal pregnancy and postpartum period.*

***Methods:*** *Transcranial Doppler ultrasound (TCD) was used to determine the systolic, diastolic and mean blood velocities in the ACA and PCA during normal gestation. The resistance (RI), was calculated. Data were analyzed using multilevel modeling, incorporating random effects models, to construct mean and percentile curves.*

***Results:*** *The 355 measurements performed on 59 patients showed decreased systolic and mean velocity in the ACA, and increased diastolic velocity in the PCA during normal pregnancy. RI in both vessels reached a maximum level in the second trimester, followed by a third trimester decrease, and a subsequent increase during the postpartum period.*

***Conclusion:*** *This study provides normative data for ACA and PCA velocity and derived parameters in pregnancy and the postpartum period. The changes in velocity suggest a redistribution of cerebral blood flow from the anterior to the posterior cerebral circulation.*

## 2.1 Introduction

The changes in central hemodynamics during pregnancy have been quite extensively studied and characterized, both with non-invasive[1] and invasive techniques.[2] However, for practical and logistic reasons (both MRI and CT are expensive and time consuming) changes in maternal cerebral hemodynamics have been less well studied. With the introduction of transcranial Doppler (TCD), intracranial cerebral blood vessels have become much more accessible and it is now possible to reliably and reproducibly study the cerebral blood flow velocity (CBFV) in the main intracranial vessels.

To date, several cross-sectional,[3, 4] and longitudinal studies[5-9] have examined maternal cerebral blood flow (CBF) during pregnancy utilizing various techniques (Doppler ultrasound, MRI) and blood vessels (middle cerebral, posterior cerebral, internal carotid). Most show a decrease in velocity (and flow with MRI) in the middle cerebral artery during pregnancy with an increase in cerebral perfusion pressure. Belfort *et al*. published normative MCA data for pregnancy and defined 5$^{th}$ and 95$^{th}$ percentiles for systolic, diastolic and mean velocity, as well as resistance index and cerebral perfusion pressure.[5] Using these normative data the same investigators studied women with preeclampsia and showed that CPP is increased in this condition, and that cerebral autoregulation in the MCA distribution is at risk, especially in women with concomitant headache.[10]

Very few investigators have studied the changes of normal pregnancy (or preeclampsia) in the other major intracranial arteries (anterior and posterior cerebral arteries) and available data is generally derived from MRI studies of flow.[7] This is most likely due to the increased difficulty in technique to reliably obtain a signal from these vessels. There is, however, good reason to study these vessels because, physiologically speaking, the posterior circulation is believed to be more vulnerable to dysfunctional cerebral autoregulation because of its relative lack of sympathetic innervation.[11] Indeed, eclampsia is hypothesized to be a cause of posterior reversible encephalopathy syndrome (PRES).[12]

To date, there are few studies that have examined the posterior cerebral artery (PCA) in pregnancy,[7, 13-16] and those that are available have usually involved patients in the third trimester.[13, 14, 16] One

longitudinal study by Zeeman[7] used MRI to determine flow in the posterior cerebral artery in normal pregnancy, but velocity data were not reported. Even less is known about the anterior cerebral artery (ACA)[13-16] in normal or abnormal pregnancy. To our knowledge, no normative data detailing changes in velocity in these vessels have been published. This situation limits our understanding of normal pregnancy, and also prevents us from comparing the data derived from patients with disease states with the expected norms.

Our primary objective was therefore to longitudinally define the normal range of the blood velocity (and selected derived parameters and ratios) in the maternal anterior and posterior cerebral arteries during normal pregnancy and postpartum.

## 2.2 Materials and methods

We conducted a prospective cohort study of normotensive, healthy pregnant patients who underwent prenatal care at our institution. Approval from our institutional review board was obtained prior to data collection, and informed consent was obtained from all participants.

We included only normotensive, non-smoking, low-risk pregnant women without cerebrovascular abnormalities, or anemia. Medication use was limited to only prenatal vitamins.

The patients were approached for enrollment during routine prenatal visits, and enrolled as early in the pregnancy as possible. Examinations were performed at the time of enrollment and then every 4 weeks thereafter during their pregnancy. The patients also returned for two examinations in the postpartum period (at 6 and 12 weeks). Patients were asked to refrain from coffee and tea in the 2 hours before their examination.

Using a standard data collection sheet, demographic characteristics, obstetrical, and neonatal outcome data were abstracted from patient interviews and available medical records. In patients who were uncertain of their last menstrual period, estimated gestational age was determined by early (first trimester) ultrasound and normal growth was confirmed by subsequent ultrasound examinations. Subjects who developed maternal pregnancy related complications (e.g. preeclampsia) were excluded from the study.

Maternal vital signs including end-tidal $CO_2$ ($EtCO_2$), urine protein, heart rate, systolic (SBP), diastolic (DBP), and mean arterial (MAP) pressures were obtained at time of each transcranial Doppler (TCD) examination. Maternal TCD examinations of the ACA and PCA were carried out using a 2 MHz pulsed, range-gated TCD probe (Medasonics Cerebrovascular Diagnositc System; Fremont, CA) with a 10 mm sample volume. The transducer was positioned at the temporal window to insonate the ACA and the PCA. Peak systolic (PSV), mean (MV), and diastolic (DV) velocities were obtained bilaterally where possible and averaged, and unilaterally if both arteries could not be insonated. A minimum of six waveforms were averaged for each parameter. Inter and intra observer variability were routinely evaluated by two examiners performing two examinations each on the same patient. Variability is known to be less than 10%. Resistance (RI) indices were calculated as: RI=(PSV-DV)/PSV

Multilevel modeling, incorporating random effects models, was used to construct mean and percentile curves.[17] All dependent variables were logarithmically transformed in order to normalize their distribution. A linearizing function of gestational age (GA) was obtained from the best fitting fractional polynomial.[17] The model consisted of a fixed component (intercept and linearizing function of GA) and a random component (random effect of intercept and random effect for GA). For all parameters, residual diagnostic was performed and -2 log likelihoods and the likelihood ratio test were used to assess model fit.[18] The $5^{th}$ and $95^{th}$ percentile were calculated by subtracting and adding 1.645×SDtot from the mean. Formulas for the GA specific means and standard deviations (SDtot) are presented in the Appendix. All data analysis was performed using SAS statistical software (version 9.3, Cary, NC).

## 2.3 Results

A total of 355 measurements was performed on 59 patients undergoing a median of 6 [2-11] examinations and these were all included in the analysis. All had a singleton pregnancy and were normotensive (MAP <105 mmHg) during all visits, and none had a history of (pregnancy induced) hypertension. The mean age during their first study was 28.8 ± 5.3 years and the median [range] for

parity was 0 [0-3]. As demonstrated in *Figure 1*, ACA systolic velocity decreased during pregnancy from 80 cm/s ($5^{th}$-$95^{th}$ centile: 63-100 cm/s) at 12 weeks to 67 cm/s ($5^{th}$-$95^{th}$ centile: 54-84 cm/s) at 40 weeks. The linear trend slope was -0.00683 cm/sec/day ( P<0.0001). Mean velocity also decreased during gestation (slope -0.00435 cm/sec/day, P < 0.0001), while diastolic velocity did not show a significant trent. Concurrently, RI showed a peak during the second trimester, and decreased towards term. (P <0.0001)

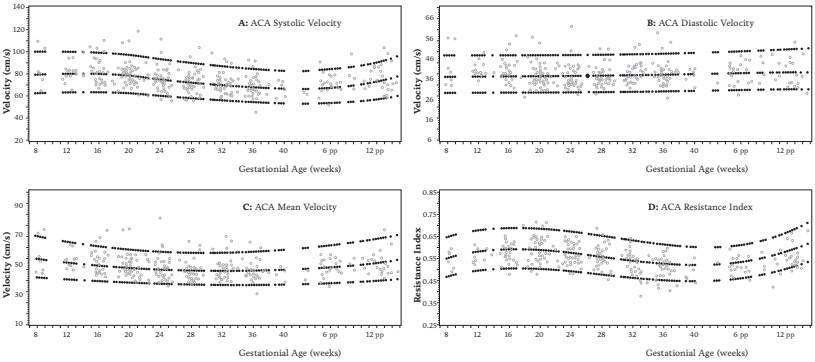


***Figure 1)*** *Anterior cerebral artery (ACA) hemodynamic parameters during pregnancy and postpartum (pp). A: systolic velocity; B: diastolic velocity; C: mean velocity; D: resistance index. (Mean, $5^{th}$ and $95^{th}$ centile)*

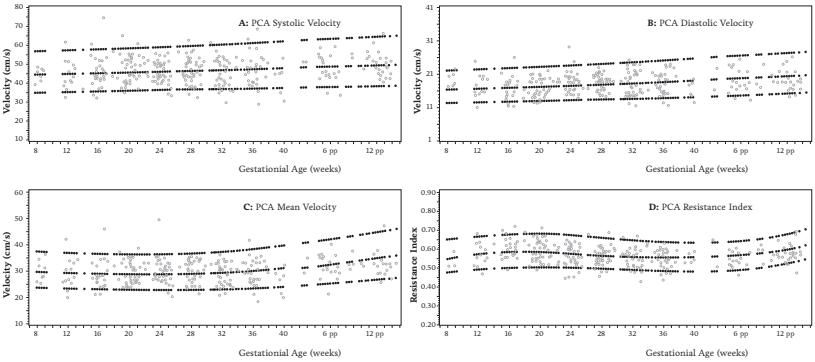


***Figure 2)*** *Posterior cerebral artery (PCA) hemodynamic parameters during pregnancy and postpartum (pp). A: systolic velocity; B: diastolic velocity; C: mean velocity; D: resistance index. (Mean, $5^{th}$ and $95^{th}$ centile)*

As shown in *Figure 2*, the velocity in the PCA progressively increased throughout the pregnancy. However, only diastolic velocity reached significance (slope +0.00456 cm/sec/day, P=0.006). PCA RI showed the same pattern as ACA, with a decrease in from the second trimester (P<0.0001).

Consistent with normal pregnancy physiology, maternal blood pressure gradually increased, and $EtCO_2$ decreased during the course of the pregnancy. (Data not shown)

With respect to the postpartum period, as demonstrated in *Figures 1 and 2* both ACA and PCA demonstrated an increase in velocity. Due to the smaller number of observations in this group (n=57, vs 286 antepartum), only ACA systolic velocity (+0.01112 cm/sec/day, P=0.019) reached significance.

## 2.4 Discussion

This study shows the normal range of blood velocity in the PCA and ACA during pregnancy, and in the postpartum period. Interestingly, we found that similar to velocity changes in the MCA,[5] there is a decrease in the ACA systolic and mean velocity during normal pregnancy, while the diastolic PCA velocity increased. The MCA changes were hypothesized being due to increased vascular distenbility. Resistance index (RI) in both vessels demonstrated a peak during the second trimester of pregnancy, followed by a third trimester decrease, with subsequent increase postpartum. The magnitude of the third trimester decrease in RI was lower for the PCA than the ACA, which is consistent with the increased velocity seen in that vessel.

The exact mechanism of the observed changes in different directions for both arteries is not known. It might be caused by a combination of changes in carbon dioxide, hormones, cytokines and other circulating factors[19] and perivascular innervations[20] and the vessels' dissimilar sensitivity to these shifts.

Pregnancy causes respiratory alkalosis and hypocapnia. As expected, we also found a decrease in $EtCO_2$ during pregnancy when compared to the postpartum period. A decrease in $EtCO_2$ is known to increase cerebrovascular resistance and decrease CBFV due to

constriction of the smaller arteries.[21, 22] The ACA did show a decrease in systolic and mean velocity during pregnancy. However, RI, often interpretated as indicator of cerebrovascular resistance, decreased in the second half of pregnancy and the diastolic velocity PCA increased. This may indicate that $EtCO_2$ is not a main determinant of cerebrovascular changes in pregnancy.

Estrogen has a vasodilatory effect on the microvasculature[23] through endothelial nitric oxide synthase.[24] Indeed, studies have demonstrated that CBF declines with the onset of menopause, and increases with hormone replacement therapy.[25, 26] By studying the effect of ovarian suppression and stimulation, a significant correlation between increased estrogen levels and increased blood flow velocity in the internal carotid artery has been shown with a concomitant decrease in cerebrovascular resistance.[27] We did find a decreased RI in both the ACA and PCA, which increased postpartum. With respect to velocity, the PCA showed signs of increased velocity, while ACA decreased.

Cipolla *et al*. have shown gestation-induced changes in endothelial and neuronal nitric oxide synthase[20] in Sprague-Dawley rats and significantly decreased nNOS expression in the anterior cortex versus posterior.[19] This regional difference might explain the different slopes seen in our study.

Our data, combined with previously published longitudinal MCA data[5] show reduced velocity in the MCA and ACA, and increased velocity in the PCA. Even though not all velocities changed significantly, extrapolating these data and assuming no change in vessel diameter (as shown by Zeeman *et al*.[7]), we suggest that during normal pregnancy there may be some degree of redistribution of cerebral blood flow from the MCA and ACA territory to that of the PCA. Studies, mainly performed in animals, have shown decreased sympathetic innervation of the posterior cerebral circulation (vertebrobasilar arteries) when compared with the anterior circulation (MCA and ACA, arising from internal carotid arteries)[11], and less effective autoregulation in pregnancy.[19]

This redistribution may explain why the posterior circulation is most vulnerable in preeclampsia and eclampsia.[28, 29] The differential changes in velocity in the ACA and PCA are interesting and suggest

that more research is needed to further elucidate the differences between the anterior and posterior circulations in pregnancy.

To the best of our knowledge, only one other study has examined PCA changes longitudinally in pregnancy, and we were unable to find any that report on longitudinal ACA changes. Zeeman and colleagues used velocity-encoded phase contrast magnetic resonance imaging in showing a decrease in PCA and MCA flow in late pregnancy (PCA at 36-38 weeks, MCA at 28-32 weeks). Flow in both arteries increased at 6 weeks postpartum when compared to the 14-16 weeks measurement.[7] We however did not find a decrease in PCA velocity during pregnancy, but did note an increase postpartum. The gestational age specific ACA velocities in our study are similar to those reported by others in cross-sectional studies.[13, 15]

Our study has some limitations, which merit discussion. Our cohort's ACA and PCA velocities progressively rose in the postpartum period, although only ACA systolic was significant. Given that we did not have pre-pregnancy data, we do not know whether this rise returned velocity to a normal pre-pregnancy level, or whether this represents a reset level following pregnancy. We also cannot comment on the timing of the return to baseline. We do not have information on the maternal hematocrit at the postpartum visits, and nor do we have data on whether or not the patients were breastfeeding, which suppresses estrogen levels. Therefore, both anemia and breastfeeding could have impacted our results. As mentioned earlier, a limitation of using TCD derived velocity to make predictions about cerebral blood flow is that a constant vessel diameter has to be assumed. Available literature shows that the MCA does not change diameter despite significant changes in $CO_2$,[30,31] and that it maintains its diameter during pregnancy.[7, 13] The PCA diameter has also been shown to maintain its diameter during pregnancy.[7] No data currently exist regarding the ACA diameter during different physiological circumstances.

This study provides the normal range in ACA and PCA velocity and derived resistance ratios, for pregnancy and the postpartum period. These nomograms may now be used to categorize and define abnormal velocity and cerebral hemodynamic status in patients with preeclampsia or other cerebrovascular abnormalities. The ability to now define the changes in cerebral hemodynamics in multiple

vessels at the same time will allow researchers a better opportunity to understand normal pregnancy physiology. Furthermore, when data from sick patients are plotted against the normative ranges, we may now be able to better define the pathologic changes in disease states that affect cerebral blood flow such as diabetes, preeclampsia and eclampsia.

## 2.5 Appendix

Assuming $Y_i$=dependent variable of interest at gestational age GAi, mean and variance of the logarithmic transformed $Y_i$, $Z_i$ at a transformed time $X_i$ are

$\mu_i = E(Z_i) = \beta_{0i} + \beta_{1i}X_i$,

$\sigma^2_i = Var(Z_i) = \sigma^2_{int} + \sigma^2_{time} X^2_i + 2\sigma_{int,time} X_i + \sigma^2_e$

where $\beta_{0i}$ . $\beta_{1i}$ are the fixed parameter estimate and $\sigma^2_{int,}$ $\sigma^2_{time}$ . $2\sigma_{int,time,}$ $\sigma^2_e$ are the estimated variance components from the multilevel analysis. The time specific values for $Y_i$ with 90% coverage is

$\exp(\mu_i \pm 1.645^*\sigma_i)$

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# CHAPTER 3

## CHANGES IN CEREBRAL AUTOREGULATION IN THE SECOND HALF OF PREGNANCY AND COMPARED TO NON-PREGNANT CONTROLS

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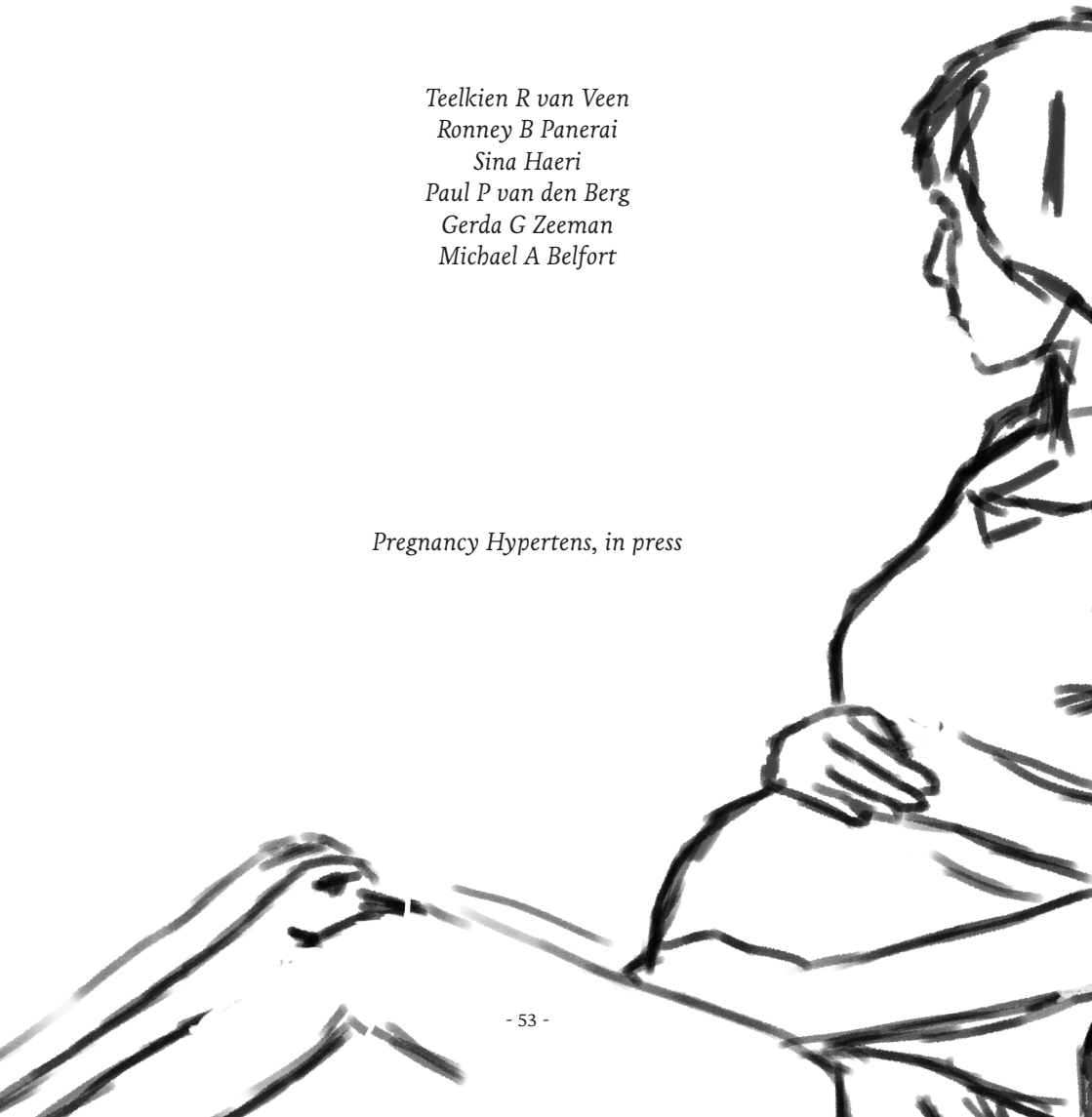
*Pregnancy Hypertens, in press*



## *Abstract*

***Objective:*** *The mechanism by which pregnancy affects the cerebral circulation is unknown, but it has a central role in the development of neurological complications in preeclampsia, which is believed to be related to impaired autoregulation.*

*We evaluated the cerebral autoregulation in the second half of pregnancy, and compared this with a control group of healthy, fertile non-pregnant women.*

***Methods:*** *In a prospective cohort analysis, cerebral blood flow velocity of the middle cerebral artery (determined by transcranial Doppler), blood pressure (noninvasive arterial volume clamping), and end-tidal carbon dioxide ($EtCO_2$) were simultaneously collected for 7 minutes. The autoregulation index (ARI) was calculated. ARI values of 0 and 9 indicated absent and perfect autoregulation, respectively. ANOVA and Pearson's correlation coefficient were used, with $p<0.05$ considered significant*

***Results:*** *A total of 76 pregnant and 18 non-pregnant women were included. The ARI did not change during pregnancy, but pregnant women had a significantly higher ARI than non-pregnant controls (ARI 6.7 ± 0.9 vs. 5.3 ± 1.4, $p<0.001$). This remained significant after adjusting for $EtCO_2$ ($p<0.001$).*

***Conclusion:*** *Cerebral autoregulation functionality is enhanced in the second half of pregnancy, when compared to non-pregnant fertile women, even after controlling for $EtCO_2$. The autoregulation did not change with advancing gestational age.*

## 3.1 Introduction

Pregnancy is characterized by major hemodynamic changes, which have been extensively studied in the systemic circulation. The adaptation of the cerebral circulation to pregnancy is unique. Several studies have examined maternal cerebral blood flow (CBF) during pregnancy using transcranial Doppler (TCD) and show a decrease in velocity in the middle cerebral artery during pregnancy with an increase in cerebral perfusion pressure and decrease in resistance index.[1-4] The exact mechanism by which pregnancy affects the cerebral hemodynamics is unknown, but is likely multifactorial, including changes in carbon dioxide ($PaCO_2$), hormones, cytokines and other circulating factors,[5] and perivascular innervation.[6]

The cerebral circulation has a central role in the development of neurological complications in preeclampsia, which is believed to be related to impaired autoregulation.[7, 8] Cerebral autoregulation is a physiological process that maintains blood flow at an appropriate level despite changes in systemic blood pressure. The autoregulatory capacity can be assessed by using a combination of TCD and continuous non-invasive blood pressure measurement,[9] and it is often expressed as the autoregulation Index (ARI), with 0 being absent and 9 perfect cerebral autoregulation.[10] In normal pregnancy ARI appears in the high normal range when compared to non-pregnant subjects. Studies in preeclampsia indicate a lower ARI when compared to normotensive pregnancy.[8] This suggests that the pregnant state in and of itself may enhance cerebral autoregulation. At what point during gestation enhancement of autoregulatory properties commences and how gestational age affects the autoregulation index is unknown. Studies reporting on non-pregnant subjects included both male and female participants in the age range of 20 to 56 years,[11-13] and are therefore not comparable to a cohort of pregnant women.

The aim of this study therefore was to evaluate the cerebral autoregulation in the second half of pregnancy, and compare this with a control group of healthy, fertile non-pregnant women.

## 3.2 Materials and Methods

We conducted a prospective cohort study including non-laboring pregnant women without a history of cerebrovascular disease, and

with an estimated gestational age (EGA) >20 weeks. The non-pregnant control group consisted of healthy women of reproductive age, who had not been recently pregnant or nursing for at least one year. Recruitment of pregnant women took place when women visited the outpatient clinic for routine prenatal care or who were admitted for observation to rule out labor. Non-pregnant controls were recruited from the hospital staff.

One trained examiner (TRVV) performed all the measurements. The study was approved by the local Institutional Review Board at Baylor College of Medicine in Houston, Texas and North Austin Medical Center in Austin, Texas, and informed written consent was obtained from each participant prior to data collection.

Inclusion criteria for both groups included maternal age greater than 18 years, absence of chronic medical illnesses, and illicit drug abuse. Women were excluded if they had a history of cerebrovascular disease, used tobacco, had gestational diabetes, used vasoactive or diabetes medication or had a blood pressure (BP) greater than 140 mmHg systolic and/or 90 mmHg diastolic at any point during their pregnancy. Furthermore, we excluded any pregnant woman who was initially included but later developed preeclampsia (n=9). Additionally, non-pregnant controls were excluded if they gave birth less than one year before the measurement or if they were lactating.

Data were entered into a standardized database with the information being collected both from the medical record and from direct patient interview. The following maternal characteristics were based on self-report: race/ethnicity, height, current and pre-pregnancy weight, smoking and alcohol and illicit substance use. Gestational age was determined by menstrual dating. In cases of uncertain menstrual dates, ultrasound estimates of gestational age were used.

Women were studied in a semi-Fowlers position in a private room. Simultaneous transcranial Doppler (TCD) evaluation of both middle cerebral arteries (MCA) was carried out using 2 MHz pulsed, range gated transcranial Doppler probes (Spencer Technologies, Seattle, WA), held in place using a head frame. If only one MCA could be found, that one side was used in the analysis. At the time of the TCD examination, brachial systolic (SBP) and diastolic (DBP) blood pressure were measured.

Blood pressure was continuously measured non-invasively using finger arterial volume clamping (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) with the servo-adjust switched off. This was subsequently calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal $CO_2$ ($EtCO_2$) was measured by infrared capnography with a nasal cannula (Nellcor Oximax N-85, Covidien, Mansfield, MA).

All data were recorded at 50 Hz, interpolated to 200 Hz and visually inspected during analysis to remove occasional large spikes. A median filter was used to remove small spikes and artifacts in the cerebral blood flow velocity (CBFV) signal. All signals were then low-pass filtered with a Butterworth filter with a cutoff frequency of 20 Hz. Mean BP, bilateral CBFV, $EtCO_2$ and heart rate were then calculated for each beat. The critical closing pressure (CrCP) and resistance-area product (RAP) were obtained using the first harmonic of BP and CBFV of each cardiac cycle.[14] The resistance index (RI) was calculated as (systolic velocity-diastolic velocity)/systolic velocity. All time-series of beat-to-beat parameters were then resampled at 5 Hz.

Cerebral autoregulation was determined from the CBFV responses to spontaneous fluctuations in mean arterial BP as described previously.[15] Segments consisting of 512 samples and 50% superposition, were transformed with the fast Fourier transform (FFT) algorithm (Welch method), to obtain the transfer function parameters coherence, gain and phase in the low frequency range (<0.1 Hz). The inverse FFT was then performed to estimate the impulse and step responses. The CBFV step response to a sudden change in ABP was compared to 10 template curves proposed by Tiecks *et al*.[10] and the best fit curve corresponded to the ARI autoregulation index.[10, 15] Measurements were rejected if coherence did not reach 0.5 for any frequency <0.25 Hz.

Baseline cerebral hemodynamic parameters are reported as the average over a 7-minute baseline recording.

Data are reported as mean and standard deviation, or median and [range] as appropriate. Non-pregnant controls were compared to the pregnant participants with a gestational age of 20-30 weeks and 31-41 weeks at time of examination using ANOVA with Bonferroni's post-hoc test or ANOVA on Ranks with Dunn's post hoc test (both

comparisons versus the non-pregnant control group). Pearson's correlation coefficient was used to investigate the relationship of the parameters of interest over gestational age, and multiple regression was used to control for $EtCO_2$. Other analyses were performed using student t test or Mann-Whitney Rank Sum test. (Sigmastat 2004, Systat Software, Richmond, CA). $p < 0.05$ was used to indicate statistical significance.

### 3.3 Results

A total of 76 pregnant (26 at 20-30 weeks' and 50 at 31-41 weeks' gestation) and 18 non-pregnant women were included. Maternal demographics were similar for both groups, except for multiple pregnancies and time of delivery *(Table 1)*. Those who delivered very preterm (EGA<32 weeks) were admitted for multiple gestation (n=6), cervical insufficiency (n=1) or preterm premature rupture of membranes (n=2). None of the women showed any sign of labor during the measurement.

Although the autoregulation index did not change during the course of pregnancy, pregnant women did demonstrate a significantly better functioning autoregulation when compared to non-pregnant controls (ARI 6.7 ± 0.9 and 6.6 ± 0.9 vs. 5.3 ± 1.4, $p<0.001$, *Figure 1*, *table 2*). Coherence was also lower in pregnancy (0.42 ± 0.13 and 0.41 ± 0.09 vs. 0.52 ± 0.09, $p<0.001$).

As expected, $EtCO_2$ was significant lower in the pregnant women. After adjusting for $EtCO_2$, the ARI was still significantly different between the groups ($p<0.001$). BP and CBFV were lower in pregnant women between 20 and 30 weeks when compared to non-pregnant controls. CrCP and RAP were not different between the groups (*Table 2*, P-value ANOVA).

The ARI of the women having multiples was not different from those having a singleton pregnancy (ARI 7.1 ± 0.3 vs. 6.6 ± 0.9, $p=0.20$).

| | EGA 20-30 weeks (n=26) | EGA 31-41 weeks (n=50) | Non-pregnant (n=18) | P value |
|---|---|---|---|---|
| **Maternal age (years)** | 28 ± 7 | 29 ± 7 | 31 ± 7 | 0.36 |
| **BMI (kg/m²)** | 29 ± 6 | 28 ± 7 | 25 ± 5 | 0.16 |
| **EGA at study (week$^{day}$)** | $26^{0}$ ± $3^{0}$ | $36^{1}$ ± $2^{2}$ | | **<0.001** |
| **EGA at delivery (week$^{day}$)** | $37^{1}$ ($27^{1}$-$41^{0}$) | $38^{6}$ ($35^{5}$-$41^{1}$) | | **<0.001** |
| **Multiple pregnancy (%)** | 5 (19%) | 1 (2%) | | **0.016** |

***Table 1) Demographic data.*** *BMI: Body mass index, for pregnant women: pre-gestational BMI; EGA: Estimated gestational age. P-value: 1-way ANOVA or t-test or Mann-Whitney-U.*
*Data are mean ± SD, median (range) or number (%)*

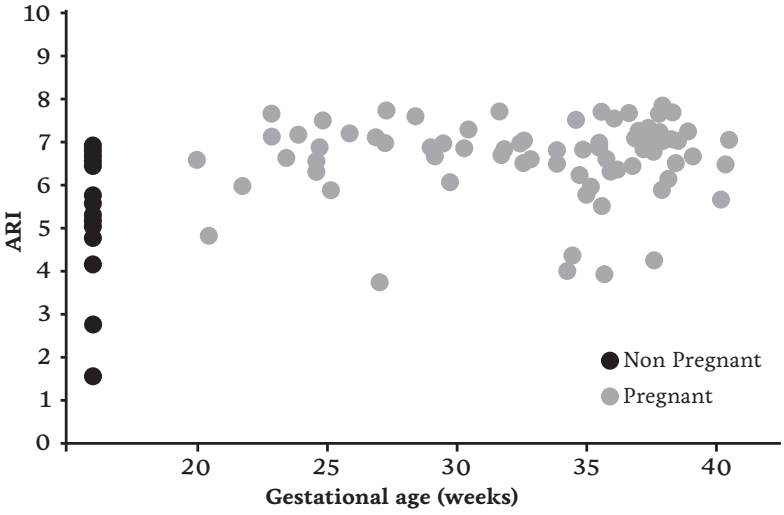



***Figure 1)*** *Autoregulation index with gestational age (●) and in non-pregnant women (●)*

| | EGA 20-30 weeks n=26 | EGA 31-41 weeks n=50 | Non pregnant n=18 | P-value (ANOVA) | P-value (Pearson) |
|---|---|---|---|---|---|
| **ARI** | **6.7 ± 0.9 P<0.001** | **6.6 ± 0.9 P<0.001** | 5.3 ± 1.4 | **<0.001** | 0.91 |
| **Phase (radians)** | **1.29 ± 0.19** | **1.28 ± 0.20** | 0.94 ± 0.11 | **<0.001** | 0.71 |
| **Coherence** | **0.42 ± 0.13 P<0.001** | **0.41 ± 0.09 P=0.005** | 0.52 ± 0.09 | **<0.001** | 0.52 |
| **Gain (cm/ mmHg.s)** | 0.74 (0.42-1.5) | 0.70 (0.26-1.36) | 0.69 (0.43-1.7) | 0.97 | 0.74 |
| **CBFV (cm/s)** | **64 ± 10 P=0.016** | **66 ± 9 P=0.036** | 72 ± 11 | **0.021** | 0.42 |
| **CrCP (mmHg)** | 11 (0-31) | 12 (0-35) | 12 (0-33) | 0.92 | 0.95 |
| **RAP (mmHg.s/ cm)** | 1.02 ± 0.25 | 1.13 ± 0.24 | 1.01 ± 0.25 | 0.072 | 0.21 |
| **RI** | 0.44 ± 0.05 | 0.42 ± 0.04 | 0.43 ± 0.05 | 0.095 | **0.029** |
| **HR (bpm)** | **87 ± 11 P<0.001** | **86 ± 12 P<0.001** | 66 ± 9 | **<0.001** | 0.69 |
| **MAP (mmHg)** | **75 ± 7 P=0.006** | 85 ± 10 | 84 ± 10 | **<0.001** | **<0.001** |
| **$EtCO_2$ (mmHg)** | **34 ± 2 P<0.001** | **33 ± 2 P<0.001** | 39 ± 1 | **<0.001** | 0.10 |

***Table 2) Hemodynamic data.*** *ARI: autoregulation index; CBFV: Cerebral blood flow velocity; MAP: Mean arterial pressure; $EtCO_2$: End-tidal $CO_2$; CrCP: Critical closing pressure; RAP: Resistance area product; RI: resistive index; Phase, coherence and gain are obtained in the low frequency range (<0.1 Hz). Data are mean ± SD, or median (range).*

Gestational age was significantly correlated with blood pressure (p<0.001, coefficient: +0.66 mmHg/week) and RI (p=0.029, coefficient -0.002 /week). ARI or any of the other parameters were not correlated with gestational age (*Table 2*, P-value Pearson).

## 3.4 Discussion

In this study, the autoregulation in the second half of pregnancy was examined and compared with observations in non-pregnant women of reproductive age. Our findings indicate that cerebral

autoregulation capacity is significantly enhanced in pregnant women, and is independent of gestational age in the second half of pregnancy.

The higher ARI seen in normal pregnancy was previously shown by our group, and hypothesized to be related to the relative hypocapnia seen in pregnancy.[8] This is known to cause physiologic vasoconstriction, a reduction in cerebral blood flow, and enhanced autoregulatory capacity.[12] However, the ARI is significantly higher in pregnancy, even after controlling for $EtCO_2$. This enhanced cerebral autoregulation is in accordance with previous studies in both human[16] and rats.[17]

One explanation for the higher ARI might be the increasing concentrations of estrogen and progesterone during pregnancy, which has important protective effects on endothelial function and cerebrovascular health.[18, 19] Estrogens increase cerebrovascular reactivity[19] and have a direct vasodilator effect on the microvasculature,[20] by, at least in part, increased expression of endothelial nitric oxide (NO) synthase (NOS).[17, 21] However, studies evaluating the role of NO on the human cerebral autoregulation are sparse, and have shown conflicting results, reporting impaired AR following NO inhibition,[22] and no effect.[23] Other factors that might be involved in the enhancement of autoregulatory capacity could be the renin-angiotensin system (RAAS),[24] perivascular innervation, vascular structure or cytokines, all known to be altered in preeclampsia.[6]

Similar to previous studies,[2-4] we also found a decrease in resistance index (RI) with advancing gestational age. While other studies also have shown a decrease in cerebral blood flow velocity (CBFV) as pregnancy advances,[2] this was not confirmed by our data. We hypothesize that this decrease mainly takes place in the first half of pregnancy, and is therefore not noticed in our study, which focused on women in the second half of pregnancy.

The strengths of this study is the inclusion of both pregnant and non-pregnant women in their reproductive age years, who were all studied in an identical setting. This study also has some limitations, which merit discussion. Using TCD, only the CBFV can be obtained, and therefore relies on the assumption that changes in CBFV are directly proportional to changes in cerebral blood flow (CBF). Available literature shows that the MCA does not change in diameter despite

significant changes in $CO_2$,[25, 26] and that it maintains its diameter during pregnancy.[27] The number of women studied in each group is unequal, with most women studied after 30 weeks of pregnancy, and patients before 20 weeks of gestation were not included. The women who were studied at EGA 20-30 weeks delivered significantly earlier and more often had a twin gestation.

The control group seems to have two outliers with very low ARI (ARI 1.6 and 2.8). Careful analysis of these subjects did not indicate erroneous measurements, and the individuals were therefore included in the analysis. However, if those would be excluded, the conclusion still holds true (ANOVA $p<0.001$). This cross-sectional study only included pregnant women in the second half of pregnancy. We can therefore not comment on the timing of the initiation of the enhancement of cerebral autoregulation, nor on the time postpartum when it returns to non-pregnant values.

In conclusion, this study demonstrates enhanced cerebral autoregulation functionality in the second half of pregnancy, when compared to non-pregnant fertile women, even after controlling for $EtCO_2$. The autoregulation did not change with advancing gestational age. The timing and the mechanism by which pregnancy enhances cerebral autoregulation functionality have yet to be explored.

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# CHAPTER 4

## CEREBRAL AUTOREGULATION IN NORMAL PREGNANCY AND PREECLAMPSIA

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*Obstet Gynecol. 2013 Nov;122(5):1064-9*

## *Abstract*

***Objective:*** *Preeclampsia is associated with altered cerebral hemodynamics, and an increased risk for cerebrovascular complications. This is believed to be related to impaired autoregulation (AR), a physiological process that maintains blood flow at an appropriate level despite changes in blood pressure. Dynamic autoregulation has yet to be examined in women with untreated preeclampsia. The aim of this study was to test the hypothesis that preeclampsia is associated with impaired cerebral dynamic autoregulation (AR).*

***Methods:*** *In a prospective cohort analysis cerebral blood flow velocity (CBFV) of the middle cerebral artery (determined by transcranial Doppler), blood pressure (determined by noninvasive arterial volume clamping), and end-tidal carbon dioxide ($EtCO_2$) were simultaneously collected during a 7-minute baseline periods of rest. The autoregulation index (ARI) was calculated. ARI values of 0 and 9 indicated absent and perfect autoregulation, respectively. Student's t-test was used, with $P<0.05$ considered significant.*

***Results:*** *Women with preeclampsia (prior to treatment, $n=20$) and their normotensive counterparts ($n=20$) did not differ with respect to baseline characteristics, except for earlier gestational age at delivery (363 (244–402) vs 392 (320–410), $P<0.001$), and higher blood pressure in women with preeclampsia. ARI during baseline was significantly reduced in preeclamptics compared with normotensive controls ($5.5\pm1.7$ vs. $6.7\pm0.6$, $P=0.004$). There was no correlation between ARI and blood pressure.*

***Conclusion:*** *Women with preeclampsia have impaired dynamic cerebral autoregulation. The fact that blood pressure does not correlate with autoregulation functionality may explain why cerebral complications such as eclampsia can occur without sudden and/or excessive elevation in blood pressure.*

## 4.1 Introduction

During pregnancy, about 2-8 % of women will be diagnosed with some form of hypertension or preeclampsia (PE). Complications of preeclampsia account for 16-38% of all maternal deaths,[1, 2] with cerebrovascular complications being the primary cause (38.7%).[1, 2] Preeclampsia has been implicated in hypertensive posterior reversible encephalopathy syndrome (PRES),[3,4] which is hypothesized to be related to impaired autoregulation (AR), leading to either over- or underperfusion of the brain.[3,5,6]

Cerebral autoregulation is a physiological process that maintains blood flow at an appropriate level, despite changes in blood pressure. Impairment of this function may explain why some patients develop cerebral edema and convulsions or cerebral hemorrhage, without significant hypertension.[7-9] In previous studies using transcranial Doppler (TCD) the lack of increased resistance and the increased cerebral blood flow velocities, coupled with increased mean arterial pressure (MAP) in preeclamptic women, have been interpreted as dysfunctional autoregulation.[10-13] Increased cerebral perfusion in preeclamptic patients was seen in studies using magnetic resonance imaging (MRI)[14] supporting the concept that preeclampsia is associated with an overperfusion syndrome and disordered cerebral autoregulation. Cipolla *et al*. conducted multiple studies on the AR in rats, and found the upper limit of AR to be slightly shifted to the right in late pregnant rats, suggesting improved autoregulation. However, only the pregnant rats had significant cerebral edema in response to acute hypertension.[15]

Transcranial Doppler (TCD) ultrasound makes it possible to study cerebral hemodynamics in pregnant women in a non-invasive fashion.[16, 17] When combined with a continuous non-invasive blood pressure measurement, dynamic cerebral AR (dCA) can be assessed at the bedside.[18] The functionality of the dynamic AR can be expressed as the Autoregulation Index (ARI), with 0 representing absent and 9 perfect cerebral autoregulation.[19] The cerebral blood flow velocity (CBFV) changes in response to BP perturbations caused by thigh cuff inflation, posture changes and drug effects have been used to study AR. However, these techniques are not suitable in pregnant patients for various logistic and practical reasons. Spontaneous fluctuation in

BP has been shown to correlate well with an induced decrease in BP with thigh cuffs for the estimation of ARI.[20] This technique has been used in the study of cerebral autoregulation in stroke,[21] hypertension and syncope.[18] Studies of dynamic autoregulation in pregnancy are scarce. Only one study used a similar approach to examine dynamic autoregulation in 3 (pre)eclamptic women who were being treated with magnesium sulfate. They found reduced phase and elevated gain, indicating impaired autoregulation.[22] No studies exist that compare normotensive pregnancy with preeclampsia before treatment with magnesium sulfate and/or antihypertensive medication. Therefore, our primary aim in this study was to test the hypothesis that preeclampsia is associated with impaired cerebral autoregulation.

## 4.2 Materials and Methods

We conducted a prospective cohort study over a six-month period (July 2012- February 2013). All subjects were non-laboring pregnant (or recently postpartum) women without a history of cerebrovascular disease. Women with preeclampsia (cases), were compared to a cohort of healthy normotensive pregnant women (controls). Preeclampsia was diagnosed according to ACOG guidelines.[23] Although all patients had blood pressures and a physiologic state that met the diagnostic criteria for preeclampsia or normotensive pregnancy at the time of inclusion in the study, the blood pressures recorded at the time of the examination were not necessarily in this range. One examiner, with adequate training (TRVV) performed all the measurements, in some cases helped by an assistant (ACG). The Baylor College of Medicine Institutional Review Board approved this study, and informed consent was obtained from each participant prior to data collection.

Women were excluded from the control group if they had received any vasoactive medication, had greater than trace proteinuria, or had a blood pressure (BP) greater than 140 mmHg systolic and/or 90 mmHg diastolic at any point during their pregnancy. Furthermore, we excluded any patient who was included as a control but who later developed a hypertensive disease. Women in the preeclamptic group were excluded if (additional, in case of superimposed preeclampsia) antihypertensive therapy was initiated or magnesium sulfate (MgSO4)

was administered <48 hour before the examination.

Data were entered into a standardized database with the information being collected both from the medical record and from direct patient interview. The following maternal characteristics were based on self-report: race/ethnicity, height, current and prepregnancy weight, smoking and alcohol and illicit substance use. Gestational age was determined by menstrual dating. In cases of uncertain menstrual dates, ultrasound estimates of gestational age were used. The presence of neurological symptoms was abstracted from the medical record.

At the time of the TCD examination, brachial systolic (SBP) and diastolic (DBP) blood pressure were measured. Patients were studied in a semi-Fowlers position in a private room. Simultaneous transcranial Doppler (TCD) evaluation of both middle cerebral arteries (MCA) was carried out using 2 MHz pulsed, range gated transcranial Doppler probes (Spencer Technologies, Seattle, WA), held in place using a head frame. If only one MCA could be found, that one side was used in the analysis. The depth of insonation was set at 45 to 65 mm with slight anterior angulation (15-30 degrees) of the probe through the temporal window. The MCA was identified using M-mode to detect the MCA/ACA bifurcation, the expected velocity and the depth.

Blood pressure was continuously measured non-invasively using finger arterial volume clamping (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) with the servo-adjust switched off. This was subsequently calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal $CO_2$ ($EtCO_2$) was measured with a nasal cannula (Nellcor Oximax N-85, Covidien, Mansfield, MA).

All data were recorded at 50 Hz, interpolated to 200 Hz and visually inspected during analysis to remove occasional large spikes. A median filter was used to remove small spikes and artifacts in the CBFV signal. All signals were then low-pass filtered with a Butterworth filter with a cutoff frequency of 20 Hz. Mean BP, bilateral CBFV, $EtCO_2$ and heart rate were then calculated for each beat. The critical closing pressure (CrCP) and resistance-area product (RAP) were obtained using the first harmonic of BP and CBFV of each cardiac cycle.[24] All signals were then resampled at 5 Hz.

Cerebral autoregulation was determined from the CBFV

responses to spontaneous fluctuations in mean arterial BP as described previously.[20] Segments consisting of 512 samples and 50% superposition, were transformed with the fast Fourier transform (FFT) algorithm (Welch method), to obtain the transfer function parameters coherence, gain and phase in the low frequency range (<0.1 Hz). The inverse FFT was then performed to estimate the impulse and step responses. The CBFV step response to a sudden change in ABP was compared to 10 template curves proposed by Tiecks *et al*.[19] and the best fit curve corresponded to the ARI autoregulation index.[19,20] Measurements were rejected if coherence did not reach 0.5 for any frequency <0.25 Hz.

Baseline cerebral hemodynamic parameters are reported as the average over the 7 minute baseline recording.

Pulsatility (PI) and resistance (RI) indices and cerebral perfusion pressure (CPP) were calculated using the averages of the velocity and maternal blood pressure data as follows:

$$PI=(PSV-DV)/MV$$

$$RI=(PSV-DV)/PSV$$

$$CPP=[MV/MV-DV](MAP-DBP)$$

All data sets were checked for normalcy of distribution (Kolmogorov-Smirnov test). Data are reported as mean and standard deviation, or median and [range] as appropriate. Analyses were performed using student t test or Mann-Whitney Rank Sum test. (Sigmastat 2004, Systat Software, Richmond, CA). $P < 0.05$ was used to indicate statistical significance.

Prior ARI studies have in general used 15-30 patients and one study showed that 45 patients are needed to show a ARI difference of 1.0;[25] however, given that these were in non-pregnant women, who are expected to have a lower baseline ARI due to higher $EtCO_2$, we could not reliably use their information for our sample size calculation. Accordingly, in this study, using a baseline mean ARI of 6.5 with an expected standard deviation of 1.0 (obtained from an initial cohort of 5 healthy pregnant women), we calculated a

necessary sample size of 16 in each group to provide approximately 80% power for detection of a 1.0 difference in group means (alpha= 0.05). However, given that prior ARI studies have used more patients, we increased our sample size to remain consistent.

## 4.3 Results

A total of 42 patients were enrolled, and 40 successfully underwent dCA evaluation. There were 20 patients in the preeclampsia group, which was made up of 12 women with mild disease (5 of whom progressed to severe disease later in pregnancy), 3 patients with severe disease at the time of inclusion, and 5 with superimposed preeclampsia. Of these 20 patients, 4 (25%) reported a history of PE or gestational hypertension in a previous pregnancy. Twenty-two women were enrolled in the control group. One patient was excluded due to insufficient coherence, and one due to frequent extrasystoles (every 4$^{th}$ to 6$^{th}$ beat). Demographic data of the 40 patients used in the analysis are presented in Table 1. The patient in the control group who delivered at 32 weeks had monoamniotic monochorionic twins.

| | **Preeclampsia (n=20)** | **Control (n=20)** | **P-value** |
|---|---|---|---|
| **Maternal age (years)** | 32 (18-43) | 30 (19-36) | 0.425 |
| **EGA at study (week$^{day}$)** | $35^{5}$ ($24^{1}$ – $40^{1}$) + 1 patient 4 days pp | $37^{0}$ ($24^{4}$ – $40^{3}$) | 0.232 |
| **Prepregnancy BMI (kg/m$^2$)** | 29 ± 8 | 27 ± 6 | 0.33 |
| **Current smoking** | 0 | 1 | 1.00 |
| **Nulliparous** | 14 | 11 | 0.514 |
| **EGA at delivery (week$^{day}$)** | $36^{3}$ ($24^{4}$ – $40^{2}$) | $39^{2}$ ($32^{0}$ – $41^{0}$) | **<0.001** |

***Table 1)*** *Demographic data*

*Figure 1* shows representative CBFV, BP and CBFV step response data from two patients. The upper panels depict 50 second segments of baseline CBFV and BP data from two patients (one with good AR

(control group, panel A) and one with impaired AR (preeclamptic group, panel C) and show the responses to a spontaneous decrease in BP. The lower panels (B and D) show the average step response of the 7 minutes baseline, with a good response (ARI = 7.0) in panel B and an abnormal response (ARI = 2.6) in panel D. In the patient with good functioning AR (panels A and B), the decrease in BP is accompanied by a smaller amplitude change in CBFV, an earlier nadir in CBFV, and a more rapid return to baseline (with an overshoot) as compared to the tracings seen in panel C. The CBFV step response, which reflects the effect of a sudden change in BP on the CBFV, also shows this fast recovery with overcorrection. The CBFV response in panel C mimics the BP, the recovery of the CBFV starts after the recovery of the BP, and the CBFV does initially not return to baseline. This pattern indicates impaired AR (ARI=2.6), and the CBFV step response reflects this by not returning to baseline.

Preeclamptic women had a significantly lower ARI *(Figure 2)*, PI and RI, and higher CPP and RAP when compared with the control patients *(Table 2)*. There was no significant correlation between ARI and PI, RI, CPP or RAP. However, the ranges of the cerebrovascular parameters were wider in the preeclamptic group, suggesting less homogeneity.

A subgroup analysis was performed comparing those preeclamptic women with an ARI above the mean ARI of the control group (ARI > 6.7), with those preeclamptic women who had an ARI at least 2 points lower (ARI <4.7).[25] The two groups, which both consisted of 6 patients, were no different in terms of the type of hypertension (3 superimposed and 3 mild PE versus 1 superimposed, 2 mild, 2 severe and 1 postpartum PE), neurological symptoms, MAP, or CBFV. However, the three patients with the worst ARI (ARI < 3), all had chronic hypertension with superimposed preeclampsia, and required ≥ 2 antihypertensive drugs to control their BP. Only one other patient had a history of chronic hypertension and antihypertensive medication use (ARI = 7.7)

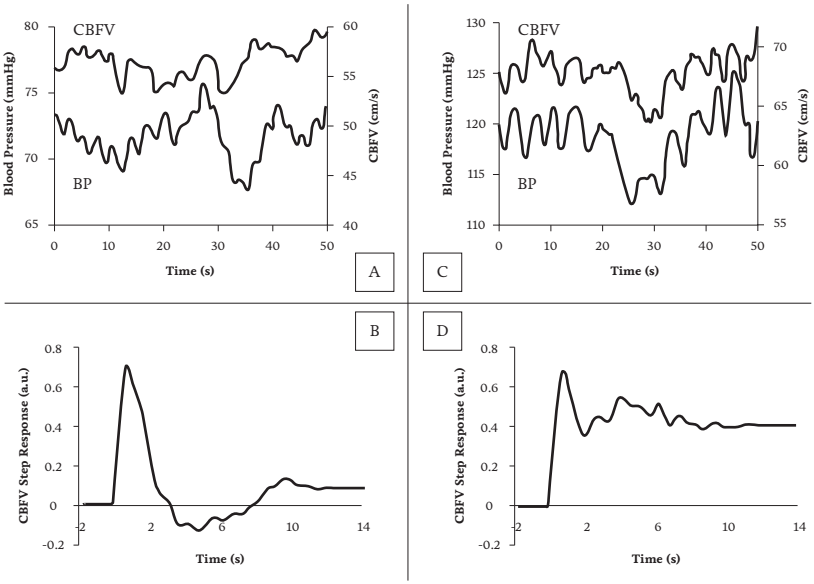


***Figure 1)*** *Example of good functioning AR (panel A) and corresponding step response (panel B, ARI =7.0 ) and impaired AR (panels C and D, ARI = 2.6) during baseline measurement.*

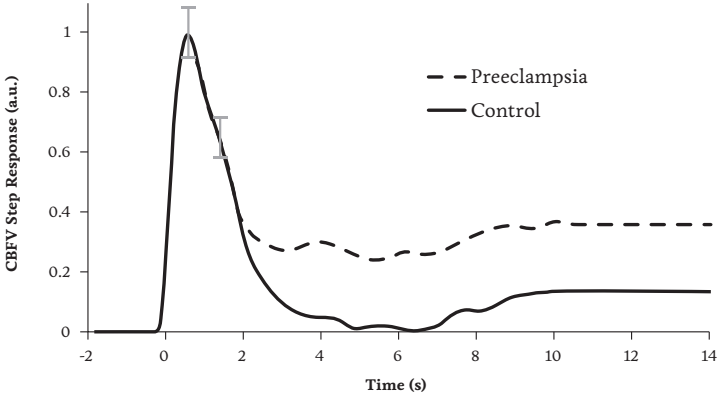


***Figure 2)*** *Average CBFV step responses of the preeclamptic (ARI =5.5 ± 1.7) and the control group (ARI = 6.7 ± 0.6). Error bars represent largest ±1 S.E.M.*

| | Preeclampsia (n=20) | Control (n=20) | P-value |
|---|---|---|---|
| **ARI** | 5.5 ± 1.7 | 6.7 ± 0.6 | **0.004** |
| **Systolic BP (mmHg)** | 139 ± 14 | 115 ± 9 | **<0.001** |
| **Diastolic BP (mmHg)** | 85 ± 10 | 67 ± 8 | **<0.001** |
| **MAP (mmHg)** | 103 ± 10 | 83 ± 8 | **<0.001** |
| **$EtCO_2$ (mmHg)** | 34 ± 2 | 34 ± 2 | 0.823 |
| **Systolic velocity (cm/s)** | 95 ± 24 | 92 ± 15 | 0.600 |
| **Diastolic velocity (cm/s)** | 59 ± 13 | 53 ± 8 | 0.121 |
| **Mean velocity (cm/s)** | 73 ± 18 | 67 ± 10 | 0.208 |
| **Resistance Index** | 0.38 ± 0.046 | 0.42 ± 0.037 | **0.006** |
| **Pulsatility Index** | 0.50 ± 0.081 | 0.58 ± 0.085 | **0.002** |
| **CPP (mmHg)** | 100 ± 23 | 74 ± 16 | **<0.001** |
| **CrCP (mmHg)** | 3.6 (0 – 40) | 9.7 (0 – 19) | 0.636 |
| **RAP ($mmHg.s.cm^{-1}$)** | 1.37 ± 0.42 | 1.13 ± 0.24 | **0.031** |

***Table 2)*** *Hemodynamic data*
*ARI: Autoregulation inde;, BP: blood pressure; MAP: mean arterial pressure; $EtCO_2$: end-tidal $CO_2$; CPP: Cerebral Perfusion Pressure; CrCP: critical closing pressure*

## 4.4 Discussion

The primary aim of this study was to test the hypothesis that preeclampsia is associated with impaired cerebral autoregulation and the data presented support the premise that preeclamptic patients have impaired dynamic cerebral autoregulation when compared to normotensive pregnant controls.

This study adds to the existing literature on cerebral hemodynamic abnormalities in preeclampsia.[3,5,6] Dynamic cerebral autoregulation is abnormal in preeclampsia, and it does not directly correlate with blood pressure. This may indirectly explain the development of eclampsia, by means of autoregulatory breakthrough and hyperperfusion, without sudden and/or excessive elevation in blood pressure. In this study only 2 preeclamptic patients had a systolic BP>160 mmHg, and none had a diastolic BP > 100 mmHg and yet dynamic cerebral autoregulation was abnormal. The mean BP in the subgroups with the best and worst ARI were not significantly different.

Aside from ARI, we also found statistically significant differences in RI, PI, RAP and CPP, but not in flow velocities or CrCP. These results are in agreement with previous studies.[10,13,26] The increase in RAP suggests an increase in the myogenic activity, while the metabolic control, as indicated by CrCP[27] was not different. The hemodynamic characteristics (e.g. ARI and blood flow velocities) of the control group were rather homogenous, the same could not be said for the cases. These hemodynamic variations reflect the wide array of presentations and varying (and multifactorial) underlying causes.

Clinical symptoms (especially visual disturbances and headache) have previously been shown to be associated with autoregulatory dysfunction in preeclampsia.[28] In the current study, those women with the most dysfunctional AR could not be identified based on clinical characteristics, (degree of proteinuria, presence of severe clinical symptoms (e.g. headache), laboratory abnormalities (data not shown), or blood pressure). However, the groups are too small to draw any definitive conclusions.

Although the normal values of ARI are not defined,[18] the ARI in the control group now described seems to be in the high normal range when compared to published data from non-pregnant subjects in an age range of 20-56 years, which have been reported to range

between 5.5 and 6.8.[25,29,30] The higher ARI might be caused by the relative hypocapnia seen in pregnancy, which is known to cause physiologic vasoconstriction, a reduction in CBF and improved autoregulatory capacity.[29]

This study has some limitations, which merit discussion. The study has a small sample size, which hindered any detailed subgroup analysis. The cases included few patients with severe laboratory abnormalities, or with neurological symptoms, which prohibited any analyses of correlation between these parameters and ARI. The data only represent a 7 minute period. While the reliability of the method has been proved in a longitudinal fashion in non-pregnant subjects, this might not hold true for preeclampsia, where blood pressure can be very labile. Due to the inherent limitations associated with the study design, assessment of ARI changes (if any) with advancing gestational age was not possible. Longitudinal studies in the future are necessary to assess this impact. Lastly, the MCA was studied because of its anatomical characteristics. However, the visual disturbances seen in preeclampsia and the fact that neuroimaging reveals that lesions consistent with PRES are generally seen in the posterior cortex implicate involvement of the posterior circulation. It is possible that local cerebral autoregulation is different in this part of the cerebrovascular system.

In conclusion, this study suggests the presence of impaired dynamic cerebral autoregulation in preeclamptic patients compared to their healthy counterparts. The paucity of data addressing the cerebral hemodynamic and autoregulation changes in preeclampsia underscore the need for further research in this area.

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# CHAPTER 5

## EFFECT OF BREATH HOLDING ON CEREBRO-VASCULAR HEMODYNAMICS IN NORMAL PREGNANCY AND PREECLAMPSIA

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## Abstract

*Preeclampsia (PE) is associated with endothelial dysfunction and impaired autonomic function, which is hypothesized to cause cerebral hemodynamic abnormalities. Our aim was to test this hypothesis by estimating the difference in the cerebrovascular response to breath holding (BH)(known to cause sympathetic stimulation) between women with preeclampsia and a group of normotensive controls.*

*In a prospective cohort analysis, cerebral blood flow velocity (CBFV) in the middle cerebral artery (transcranial Doppler), blood pressure (BP, noninvasive arterial volume clamping), and end-tidal carbon dioxide ($EtCO_2$) were simultaneously recorded during a 20 second breath hold maneuver. CBFV changes were broken down into standardized subcomponents describing the relative contributions of BP, cerebrovascular resistance index (CVRi), critical closing pressure (CrCP) and resistance area product (RAP). The area-under-the-curve (AUC) was calculated for changes in relation to baseline values.*

*A total of 25 preeclamptic (prior to treatment), and 25 normotensive women in the second half of pregnancy were enrolled, and respectively 22 and 21 patients were included in the analysis. The increase in CBFV and $EtCO_2$ was similar in both groups. However, the AUC for CVRi and RAP during BH was significantly different between the groups (3.05±2.97 vs.-0.82±4.98, $P=0.006$ and 2.01±4.49 vs.-2.02±7.20, $P=0.037$), indicating an early, transient increase in CVRi and RAP in the control group, which was absent in PE. BP had an equal contribution in both groups.*

*Women with preeclampsia have an altered initial CVRi response to the BH maneuver. We propose that this is due to blunted sympathetic or myogenic cerebrovascular response in women with preeclampsia.*

## 5.1 Introduction

Preeclampsia (PE) is a systemic disease occurring in the second half of pregnancy, complicating 2–8% of pregnancies, and among the leading causes of maternal mortality and severe morbidity. PE is generally defined as new hypertension and proteinuria. The exact pathophysiology of preeclampsia remains unclear, but leading hypotheses are based on disturbed placental function in early pregnancy, causing endothelial dysfunction that can affect several organs, including the brain.[1] Cerebral manifestations include headache, hypertensive encephalopathy, eclampsia, and cortical blindness, and are believed to be caused by impaired cerebral blood flow regulation.[2] Cerebral autoregulation (AR) is the ability of the cerebral vasculature to maintain adequate cerebral perfusion despite changes in blood pressure, and can be affected by a variety of factors such as partial pressure of carbon dioxide ($PaCO_2$), extreme hypo- or hypertension, mental activation and intracranial pressure.

Deep breath holding is associated with complex chemical ($PaCO_2$), mechanical (changes in BP and heart rate (HR)), and neural consequences (autonomic nervous system), all of which affect cerebral blood flow (CBF). Deep breath holding induces changes in the autonomic nervous system, which is thought to result in a redistribution of blood flow to the cerebral circulation.[3, 4] This physiological response is known as the diving response, and characterized by a rapid onset bradycardia.[3]

The hypercapnia that occurs as a result of breath holding leads to cerebral vasodilation and increased CBF, and reflects the ability of the vascular endothelium to adapt to changes in metabolic activity. This vasoreactivity is impaired in patients who have a predisposition to cerebrovascular diseases, such as hypertension,[5, 6] diabetes[5, 7] or carotid artery stenosis.[5, 8] The proposed hypothesis to explain the response has to date been based on endothelial dysfunction.[5, 7]

Previous studies on vasoreactivity in women with preeclampsia have shown conflicting results, with either impaired[9, 10] or unaffected[11] vasoreactivity. However, none of these studies measured the CBF velocity (CBFV) or the blood pressure (BP) continuously, and thus lacked the ability to define the temporal pattern of the physiologic changes associated with hypercapnia.

Using multivariate models of the CBFV response to breath holding, the independent contributions of (a) BP and cerebrovascular resistance (CVR) and (b) BP, critical closing pressure (CrCP) and resistance area product (RAP), to changes in CBFV can be analyzed. While resistance (CVR) has traditionally been used to indicate vasodilation or vasoconstriction, a two-parameter model, using CrCP and RAP can give more information, possibly reflecting different regulatory pathways in the cerebral circulation. It has been suggested that CrCP is mainly influenced by metabolic pathways, while RAP is thought to largely reflect myogenic activity in response to BP transients.[12, 13] By separating the different systemic and cerebral influences that account for the CBF response, more insight into the pathophysiology of preeclampsia will be gained.

Therefore, our primary aim in this study was to test the hypothesis that preeclampsia is associated with an altered cerebrovascular response to breath holding when compared to their normotensive counterparts.

## 5.2 Methods

We conducted a prospective cohort study in non-laboring pregnant women without a history of cerebrovascular disease. Women with preeclampsia (cases), were compared to a cohort of healthy normotensive pregnant women (controls).

Patients were recruited and tested at Texas Children's Pavilion for Women in Houston and North Austin Maternal-Fetal Medicine in Austin, Texas, either at the time of admission to the hospital for management of preeclampsia, or at the time of routine prenatal care. Preeclampsia was diagnosed according to ACOG guidelines.[14]

One examiner (TRVV) performed all the measurements. The Institutional Review Boards at Baylor College of Medicine in Houston, Texas and North Austin Medical Center in Austin, Texas approved the study, and informed consent was obtained from each participant prior to data collection.

Women were excluded from the control group if they had a history of a chronic disease, had received any vasoactive medication, had greater than trace proteinuria, or had blood pressure (BP) greater than 140 mmHg systolic and/or 90 mmHg diastolic at any point

during their pregnancy. Inability to perform the breath holding maneuver, or an incorrectly performed maneuver were also exclusion criteria. Furthermore, we excluded any patient who was included as a control but who later in pregnancy developed a hypertensive disease or diabetes. Women with preeclampsia were excluded if antihypertensive therapy was initiated, or magnesium sulfate (MgSO4) was administered <48 hour before the examination.

Data were entered into a standardized database with background information being collected both from the medical record and from direct patient interview. The following maternal characteristics were based on self-report: race/ethnicity, height, current and pre-pregnancy weight, smoking, alcohol, and illicit substance use. Gestational age was determined by menstrual dating. In cases of uncertain menstrual dates, ultrasound estimates of gestational age were used. The presence of neurological symptoms was abstracted from the medical record.

At the time of the TCD examination, brachial systolic (SBP) and diastolic (DBP) blood pressure were measured. Patients were studied in a semi-Fowlers position in a private room. Simultaneous transcranial Doppler (TCD) evaluation of both middle cerebral arteries (MCA) was carried out using 2 MHz pulsed, range gated transcranial Doppler probes (Spencer Technologies, Seattle, WA), held in place using a head frame. If only one MCA could be found, that one side was used in the analysis. Blood pressure was continuously measured non-invasively using finger arterial volume clamping (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) with the servo-adjust control switched off. This was subsequently calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal $CO_2$ ($EtCO_2$) was measured with a nasal cannula (Nellcor Oximax N-85, Covidien, Mansfield, MA), and linearly interpolated at the end of each expiratory phase.

After an acclimatization period of at least 10 minutes, patients were asked to take a breath and hold it for 20 seconds (or for as long as possible if they were unable to achieve a 20 second breath hold). This was followed by a 2 minute recovery period during which they breathed normally. The initial small BP peak at the start of the BH maneuver was used as point of synchronism and as the beginning of the 20 second analysis interval.

All data were recorded at 50 Hz, interpolated to 200 Hz and visually inspected during analysis to remove occasional large spikes. A median filter was used to remove small spikes and artifacts in the CBFV signal. All signals were then low-pass filtered with a Butterworth filter with a cutoff frequency of 20 Hz. Mean BP, bilateral CBFV, $EtCO_2$ and heart rate were then calculated for each beat. The cerebrovascular resistance index (CVRi) was estimated by the ratio meanABP/meanCBFV of each cardiac cycle and critical closing pressure (CrCP) and resistance-area product (RAP) were obtained using the first harmonic of BP and CBFV.[15] All signals were then resampled at 5 Hz.

To identify the different systemic and cerebral contributions to the total change in CBFV induced by breath holding, the total percentage change in CBFV was broken down into standardized subcomponents describing the relative contributions of BP, CVRi, CrCP and RAP. The subcomponent analysis was represented in two ways 12: 1) as the sum of simultaneous changes in BP, CrCP and RAP; and 2) as the sum of changes in BP and CVRi, resulting in

***1)*** $\Delta v = V_{BP} + V_{CrCP} + V_{RAP}$ and

***2)*** $\Delta v = V_{BP} + V_{CVRi}$

where Δv is the change in CBFV in percent of baseline values and $V_{ABP}$, $V_{CrCP}$, $V_{RAP}$ and $V_{CVRi}$ are its subcomponents due to concomitant changes in ABP, CrCP, and RAP, respectively, which are also expressed in % change in velocity.[13]

With this analysis, RAP, CVRi and CrCP will appear inverted since their increases will lead to reductions in CBFV.

The area-under-the-curve (AUC) of these parameters was calculated for changes in relation to baseline values. A low-pass filter with a cutoff frequency of 0.15 Hz was used for the graphs. The baseline values reflect the average over a one-minute period before the breath holding maneuver.

All data sets were checked for normalcy of distribution (Kolmogorov-Smirnov test). Data are reported as mean and standard deviation, or median and [range] as appropriate. Analyses were performed

using student t test, Mann-Whitney Rank Sum test or Fisher's exact test. (Sigmastat 2004, Systat Software, Richmond, CA). A P-value of < 0.05 was used to indicate statistical significance.

## 5.3 Results

A total of 25 patients were enrolled in each group and included in the analysis. After visual inspection of the heart rate response, 3 women with preeclampsia and 4 normotensive women were excluded because they showed an acceleration in HR during the breath holding maneuver, suggesting an incorrectly performed breath hold maneuver. One patient with severe post-partum preeclampsia was excluded to eliminate the effect higher $PaCO_2$ postpartum when compared to pregnancy. The preeclampsia group was made up of 12 women with mild disease (3 of whom progressed to severe disease later in pregnancy), 3 patients with severe disease at the time of inclusion, and 6 with superimposed preeclampsia. Four patients with PE had diabetes, all were monitored very closely, 3 were diet controlled and none had any signs of end-organ damage. The two groups did not differ with respect to demographic features except for earlier gestational age at delivery in the subjects with preeclampsia *(Table 1)*.

| | **Preeclampsia (n=21)** | **Control (n=21)** | **P-value** |
|---|---|---|---|
| **Maternal age (years)** | 30.9 ± 6.2 | 30.5 ± 4.9 | 0.83 |
| **Pre-gestational BMI (kg/m²)** | 30.7 ± 8.2 | 26.3 ± 6.0 | 0.06 |
| **Current smoking (n (%))** | 0 (0%) | 1 (4%) | 1.00 |
| **Nulliparous (n (%))** | 14 (67%) | 13 (62%) | 1.00 |
| **Multiple gestation (n (%))** | 5 (24%) | 1 (4%) | 0.18 |
| **Diabetes Mellitus (n (%))** | 4 (19%) | 0 | 0.11 |
| **EGA at study (week$^{day}$)** | $35^{4}$ ($24^{1}$ – $40^{1}$) | $37^{2}$ ($24^{4}$ – $40^{3}$) | 0.07 |
| **EGA at delivery (week$^{day}$)** | $35^{5}$ ($24^{3}$ – $40^{2}$) | $39^{0}$ ($32^{0}$ – $41^{1}$) | **<0.001** |

***Table 1)*** *Demographic data BMI: body mass index; EGA: estimated gestational age; PP: postpartum Data are median (range), mean ± standard deviation, or n(%).*

Baseline CBFV, BP, CVRi and RAP were significantly higher in women with preeclampsia *(Table 2)*.

| | Preeclampsia (n=21) | Control (n=21) | P-value |
|---|---|---|---|
| **CBFV (cm/s)** | 76.0 ± 18.0 | 65.5 ± 8.4 | **0.016** |
| **CVRi (mmHg.s.cm$^{-1}$)** | 1.50 ± 0.39 | 1.28 ± 0.24 | **0.039** |
| **CrCP (mmHg)** | 3.71 (0 – 40) | 10.6 (0 – 25) | 0.58 |
| **RAP (mmHg.s.cm$^{-1}$)** | 1.37 ± 0.44 | 1.14 ± 0.27 | **0.033** |
| **MAP (mmHg)** | 108.3 ± 12.6 | 82.0 ± 9.4 | **<0.001** |
| **HR (bpm)** | 87.2 ± 8.6 | 84.5 ± 11.9 | 0.40 |
| **$EtCO_2$ (mmHg)** | 33.6 ± 2.1 | 34.5 ± 1.6 | 0.14 |

***Table 2)*** *Baseline hemodynamic values. CBFV: Cerebral blood flow velocity; CVRi: cerebrovascular resistance index; CrCP: Critical closing pressure; RAP: resistance area product; MAP: mean arterial pressure; HR: heart rate; $EtCO_2$: End tidal carbon dioxide. Data are median (range) or mean ± standard deviation.*

In both groups, the breath holding maneuver resulted in a typical pattern, consisting of bradycardia *(Figure 1)*, followed by the following pattern in BP and CBFV: initial increase, subsequent decrease, and final slow rise preceding the peak immediately after the end of breath hold *(Figure 2)*.

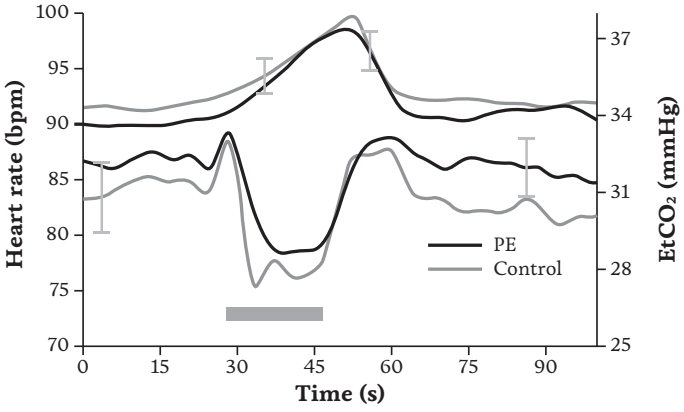


***Figure 1)*** *Changes in heart rate (HR) and end-tidal $CO_2$ ($EtCO_2$) during the breath hold maneuver (gray bar) for the two groups BPM: beats per minute; Gray bar: breath hold maneuver.*

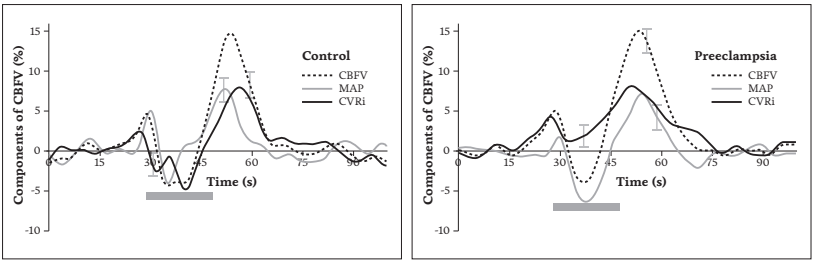


***Figure 2)*** *Group average components of CBFV change during breath holding in percentage change in the control group (A) and the preeclampsia group (B) for the CVRi model. The change in CBFV is the sum of simultaneous changes in MAP and CVRi. CBFV: cerebral blood flow velocity; MAP: mean arterial pressure; CVRi: Cerebrovascular resistance index; Gray bar: breath hold maneuver. Error bars represent largest ± 1 S.E.M.*

The change in CBFV (Δv), expressed in percent of baseline values, during breath holding for each group is presented in *Figures 2 and 3*. This change is the sum of simultaneous changes in BP and CVRi *(Figure 2)* or BP, CrCP and RAP *(Figure 3)*.

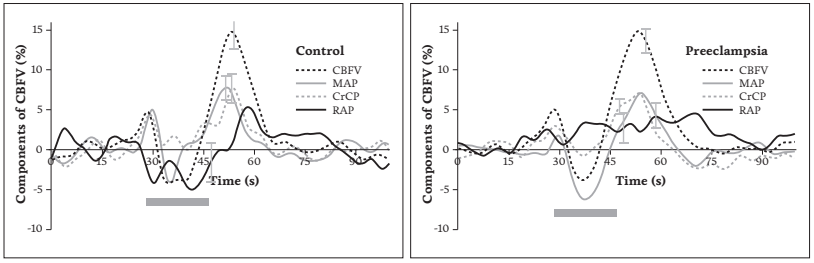


***Figure 3)*** *Group average components of CBFV change during breath holding in percentage change in the control group (A) and the preeclampsia group (B) for the CrCP+RAP model. The change in CBFV is the sum of simultaneous changes in BP, CrCP and RAP. CBFV: cerebral blood flow velocity; MAP: mean arterial pressure; CrCP: Critical closing pressure; RAP: resistance area product; Gray bar: breath hold maneuver. Error bars represent largest ± 1 S.E.M.*

BP had an equal contribution in both groups (-1.84 ± 4.46 vs. 0.70 ± 5.24, P=0.08), but the AUC for CVRi and RAP during BH were significantly different between the groups (3.05 ± 2.97 vs. -0.82 ± 4.98, P=0.006 and 2.01 ± 4.49 vs. -2.02 ± 7.2, P=0.037, *Table 3*).

| | Preeclampsia (n=21) | Control (n=21) | P-value |
|---|---|---|---|
| **CBFV (%)** | 1.24 ± 3.5 | -0.02 ± 4.3 | 0.43 |
| **CVRi (%)** | 3.05 ± 2.97 | -0.82 ± 4.98 | **0.006** |
| **CrCP (%)** | 1.33 ± 3.17 | 1.38 ± 3.76 | 0.88 |
| **RAP (%)** | 2.01 ± 4.49 | -2.02 ± 7.2 | **0.037** |
| **MAP (%)** | -1.84 ± 4.46 | 0.70 ± 5.24 | 0.08 |
| **$EtCO_2$ (mmHg)** | 35.9 ± 2.4 | 36.5 ± 2.2 | 0.59 |

***Table 3)*** *Area under the curve for subcomponents of CBFV variation during breath holding. For abbreviations, see Table 1*

*Figure 4* shows the average percentage of the CVRi contribution for the two groups, in absolute values (A) and as a component of the CBFV change (B), with the AUC indicated by the shaded areas. This figure also shows a second transient increase in CVRi in the control group, leading to a negative reflection in the subcomponent analysis (increased CVRi decreases the CBFV, *Figure 4B*). This transient change was absent in women with preeclampsia.

Visual inspection of the measurements showed that 81% of the tracings in the control group had a second peak, while only 41% of the tracings of women with preeclampsia demonstrated this peak P=0.005).

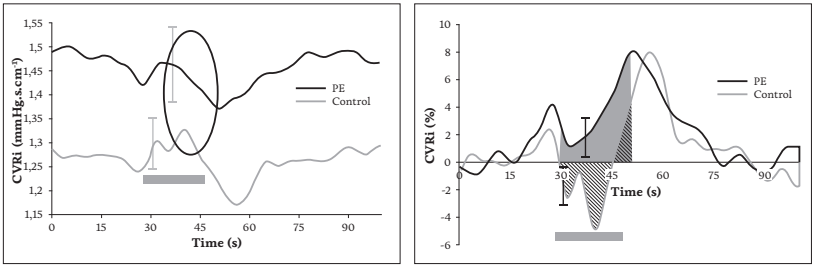


***Figure 4)*** *Group averages of CVRi during breath holding.*
*A: absolute CVRi values, showing an absent transient increase in the PE group. B: Subcomponent analysis of CVRi, indicating the percentage contribution of CVRi to the CBFV response. Positive changes in VRAP and VCrCP are caused by reductions in RAP and CrCP, leading to increases in CBFV*
*The shaded areas indicate the area under the curve used for analysis. CVRi: Cerebrovascular resistance index; PE: Preeclampsia*

## 5.4 Discussion

This study shows that women with preeclampsia have an altered cerebrovascular response to breath holding when compared to normotensive pregnant women. Even though the CBFV and BP response, and the peak CBFV, BP and CVRi are similar in both groups, the group with preeclampsia lacks a transient increase in both CVRi and RAP during the initial phase of the BH maneuver. We hypothesize that this is due to a blunted sympathetic or impaired myogenic cerebral vasoconstriction response in women with preeclampsia.

Besides influencing $PaCO_2$, deep breath holding also affects the sympathetic nervous system via the diving reflex.[3] This reflex is characterized by peripheral sympathetic stimulation, leading to vasoconstriction and increased blood pressure (BP) along with a parasympathetic induced heart rate reduction,[3] which can also be elicited by immersion of the face in cold water. The combination of apnea with stimulation of facial cold receptors attenuates the response.[3] Although the exact role of the autonomic nervous system on the regulation of CBF remains controversial,[16] recent studies do suggest an autonomic, mainly sympathetic, role in cerebral blood flow control.[17, 18]

Little is known about the CBF response to the diving reflex. $PaCO_2$ is a potent vasodilator, for which the vasculature of the brain is more sensitive than the systemic circulation,[3, 4, 19, 20] causing a redistribution of blood to the brain. The effect of BP, sympathetic stimulation and CVR in this sequence of events is largely unknown. Palada *et al*. saw an initial increase in CVRi during breath holding, before becoming negative.[20] Brown *et al*. applied a cold stimulus in eucapnic conditions, and showed an increase in CVRi until the stimulus was removed.[21] They interpreted this as sympathetic induced vasoconstriction.

In this study, the transient increase in CVRi and RAP in the early, eucapnic stage of breath holding might indicate a transient sympathetic effect initiated by the diving reflex, before the effect of the increased $PaCO_2$ dominates, causing vasodilation and thus decreasing CVR. The patients with preeclampsia did not show this initial response, and the CVRi seemed to be mainly influenced by the BP and $PaCO_2$. The precise mechanism for this cannot be determined

from our study, but potential explanations are a diminished sensitivity of the cerebral vasculature to sympathetic activity or impairment of the vessels' response to this activity (possibly due to increased sympathetic activity or increased CVRi at baseline).[22]

Another explanation could be impairment of the myogenic pathway. Salinet *et al*. showed a similar response in patients with a recent ischemic stroke.[23] In those patients, the RAP followed the BP, instead of the metabolic demand during passive arm movement, while the CrCP response was similar to controls.[23] The authors interpreted this as the result of a damaged myogenic pathway.[23]

The similar subcomponent peak of CrCP between the groups in our study suggests that the metabolic pathway is intact, at least during the relatively small demand of a short breath hold. The contribution of the metabolic versus myogenic effect of sympathetic stimulation is not known.

One of the strengths of this study is the inclusion of patients with PE who were not treated with magnesium sulfate or had recent changes in antihypertensive therapy at time of the measurement. This study has some limitations, which also merit discussion. The small sample size hindered any detailed subgroup analysis. The cases included few patients with severe laboratory abnormalities, or with neurological symptoms, which precluded any analyses of correlation between these parameters and the CVRi pattern.

Another potential limitation relates to the measurement technology that was used to measure CBFV (TCD) and BP (finger arterial volume clamping). TCD measured blood flow-velocity can only reliably be interpreted as CBF if the diameter of the MCA remains constant. However, studies have shown that the MCA does not change diameter despite significant changes in $CO_2$.[24, 25] If the MCA diameter were reduced, it would lead to an overestimation of the CBFV and RAP changes, but changes in CrCP would not be affected. Estimates of cerebral hemodynamic parameters from noninvasive BP measurement in the finger are comparable to those estimated using intra-arterial measurements in the ascending aorta.[26] However, in the case of peripheral vasomotor regulation during breath holding, and the subsequent sympathetic stimulation of the diving reflex, this might not be the case. This is because the diving reflex has a graded

response and may cause a greater vasoconstrictor response in the fingers than in the forearm.[27]

In conclusion, this study suggests that the cerebral circulation of women with preeclampsia has a reduced vasoconstrictor response, similar to what is seen in acute stroke patients. Further research is needed to get a better understanding of the influence of the sympathetic nervous system and the myogenic pathways on the cerebral complications seen in preeclampsia.

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# CHAPTER 6

## CEREBRAL AUTOREGULATION IN DIFFERENT HYPERTENSIVE DISORDERS OF PREGNANCY

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*Am J Obstet Gynecol. 2015 Apr;212(4):513.e1-7*

## Abstract

***Objective:*** *Cerebrovascular complications associated with hypertensive disorders of pregnancy (preeclampsia (PE), chronic hypertension (CHTN) and gestational hypertension (GHTN)) are believed to be associated with impaired cerebral autoregulation (AR), a physiological process that maintains blood flow at an appropriate level despite changes in blood pressure. The nature of AR dysfunction in these conditions is unclear. We therefore evaluated AR in 30 patients with PE, 30 with CHTN and 20 with GHTN, and compared them to a control group of 30 normal pregnant women.*

***Study design:*** *The autoregulation index (ARI) was calculated using simultaneously recorded cerebral blood flow velocity in the middle cerebral artery (transcranial Doppler ultrasound), blood pressure (noninvasive arterial volume clamping), and end-tidal carbon dioxide during a 7-minute period of rest. ARI values of 0 and 9 indicate absent and perfect autoregulation, respectively. Statistics: ANOVA with Bonferroni test versus control group. Data are presented as mean ± SD.*

***Results:*** *ARI was significantly reduced in PE (ARI 5.5 ± 1.6, $P = 0.002$) and CHTN (5.6 ± 1.7, $P = 0.004$) but not in GHTN (6.7 ± 0.8, $P = 1.0$) when compared to controls (6.7 ± 0.8). ARI was more decreased in patients with CHTN who subsequently developed PE than in those who did not (3.9 ± 1.9 vs. 6.1 ± 1.2, $P = 0.001$). This was not true for women with GHTN or controls who later developed PE.*

***Conclusion:*** *Pregnant women with CHTN or PE (even after excluding superimposed PE) have impaired AR when compared to women with GHTN or normal pregnancy. Whether the decreased ARI in patients with CHTN who later develop PE is due to preexistent differences or early affected cerebral circulation remains to be determined.*

## 6.1 Introduction

Hypertension is one of the most common medical complications of pregnancy, accounting for 16-38% of all maternal deaths.[1, 2] While multiple maternal organs can be affected, cerebrovascular involvement is one of the more serious ones as it can lead to death or long term morbidity due to cerebrovascular hemorrhage or edema.[1, 2] The cerebral manifestations in these patients are similar to those seen in the posterior reversible encephalopathy syndrome (PRES)[3, 4], which is hypothesized to be related to impaired autoregulation (AR), leading to either over- or underperfusion of the brain.[3, 5, 6]

Hypertensive disorders of pregnancy range in a spectrum from chronic hypertension (CHTN) to gestational hypertension (GHTN), preeclampsia (PE), and super-imposed preeclampsia in the setting of chronic hypertension (SiPE). Women with CHTN have an increased risk of developing SiPE. The incidence has been reported to be between 12 and 29%[7-9], although women with severe CHTN in the first trimester have been reported to go on to SiPE in up to 52% of cases.[10] The risk for cerebrovascular complications during pregnancy is increased with all hypertensive disorders[11-13], but is most pronounced with severe preeclampsia and SiPE.[12, 13] These complications are believed to be caused by impaired cerebral autoregulation, related to endothelial dysfunction.[14]

Cerebral autoregulation (AR) is the ability of the cerebral vasculature to maintain adequate cerebral perfusion despite changes in blood pressure. The cerebral AR can be assessed by using a combination of transcranial Doppler (TCD) and continuous non-invasive blood pressure measurement.[15] The functionality of the AR can be expressed as the Autoregulation Index (ARI), with 0 being absent and 9 perfect cerebral autoregulation.[16] This ARI has been shown to be lower in PE when compared to normotensive controls.[5] The ARI was independent of blood pressure and clinical symptoms, which may explain why cerebral complications such as eclampsia and cerebrovascular hemorrhage can occur without sudden and/or excessive elevation in blood pressure.[5] The ARI of the other hypertensive disorders in pregnancy is not known. Based on the increased risks of cerebrovascular complications seen in pregnancies complicated by CHTN and PE, but not in GHTN, we hypothesize that the AR is

impaired in CHTN (as has been shown for PE), but not in GHTN.

Consequently, the aim of this study was to evaluate cerebral autoregulation in hypertensive disorders of pregnancy (SiPE, PE, CHTN and GHTN), and compare this with a control group of normal pregnant women. Furthermore, we measured the more traditional parameters cerebral blood flow velocity, critical closing pressure and resistance-area-product to gain additional insight in the pathophysiology.

## 6.2 Materials and Methods

We conducted a prospective cohort study in non-laboring pregnant women recruited between 20 and 41 weeks gestation. The Institutional Review Boards at Baylor College of Medicine in Houston, Texas and North Austin Medical Center in Austin, Texas approved this study, and informed consent was obtained from each participant prior to data collection.

Patients were recruited and tested at Texas Children's Pavilion for Women in Houston and North Austin Maternal-Fetal Medicine in Austin, Texas, either at the time of admission to the hospital for management of a hypertensive disorder, or at the time of routine prenatal care. Inclusion criteria were maternal age greater than 18 years and absence of a history of cerebrovascular disease or epilepsy. Hypertensive diagnoses were based on ACOG guidelines.[17, 18] Exclusion criteria consisted of smoking, drugs use and the initiation of antihypertensive therapy or treatment with magnesium sulfate <48 hour before the examination.

Using a standard data collection sheet, demographic characteristics and obstetrical data were abstracted from patient interviews and medical records. The following maternal characteristics were based on self-report: race/ethnicity, height, current and pre-pregnancy weight, smoking and alcohol and illicit substance use. Gestational age was determined by menstrual dating. In cases of uncertain menstrual dates, ultrasound estimates of gestational age were used. Patients were followed until 6 weeks postpartum.

At time of TCD examination, brachial systolic and diastolic blood pressures were measured. With the patients in semi-Fowlers position, bilateral maternal transcranial Doppler (TCD) examinations

of the middle cerebral artery (MCA) were carried out using 2 MHz pulsed, range gated transcranial Doppler probes (Spencer Technologies, Seattle, WA), held in place using a head frame.

Blood pressure was continuously measured non-invasively using finger arterial volume clamping (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) with the servo-adjust switched off, and was afterwards calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal $CO_2$ ($EtCO_2$) was measured with a nasal cannula (Nellcor Oximax N-85, Covidien, Mansfield, MA), and linearly interpolated at the end of each expiratory phase.

Patients were measured only once for a period of 7 minutes. All data were recorded at 50 Hz, interpolated to 200 Hz and visually inspected during analysis to remove large spikes. A median filter was used to remove small spikes and artifacts in the cerebral blood flow velocity (CBFV) signal. All signals were then low-pass filtered with a Butterworth filter with a cutoff frequency of 20 Hz.[19] Mean BP, bilateral CBFV, $EtCO_2$ and heart rate were then calculated for each beat. The critical closing pressure (CrCP) and resistance-area product (RAP) were obtained using the first harmonic of BP and CBFV of each cardiac cycle.[20] All signals were then resampled at 5 Hz.[19]

Cerebral autoregulation was determined from the CBFV responses to spontaneous fluctuations in mean arterial BP as described previously.[19] Segments of 512 samples and 50% superposition were transformed with the fast Fourier transform (FFT) algorithm, using the Welch method to obtain the transfer function parameters coherence, gain and phase in the low frequency range (<0.1 Hz). The inverse FFT was then performed to estimate the impulse and step responses. The CBFV step response to a sudden change in BP was compared to 10 template curves proposed by Tiecks *et al*.[16] and the best-fit curve corresponded to the ARI autoregulation index. A value of ARI=9 represents the best observed cerebral autoregulation.[16]

Measurements were rejected if coherence did not reach 0.5 for any frequency <0.25 Hz. Reported baseline CBFV, BP, RAP and CrCP were the averages over the 7 minute baseline recording.

All data sets were checked for normalcy of distribution (Sigmastat 2004, Systat Software, Richmond, CA). Data are reported

as mean and standard deviation, or median with the corresponding range as appropriate. Analyses were performed using ANOVA with Bonferroni's post-hoc test, ANOVA on Ranks with Dunn's post hoc test (both comparisons versus the control group) and a second analysis using multiple linear regression including pre-pregnancy BMI and gestational age at study was performed to control for these potential confounders.

Chi-square without Yates correction was used for analysis between groups. Student t test or Mann-Whitney Rank Sum test were used for subgroup analysis. Univariate regression analysis was used to assess the relationship between autoregulation parameters and blood pressure. A two tailed $p < 0.05$ was used to indicate statistical significance.

## 6.3 Results

A total of 30 patients with preeclampsia (PE, 23 new onset, 7 superimposed PE (SiPE, confirmed PE at the time of measurement)), 30 with chronic hypertension (CHTN, 16 with and 14 without antihypertensive treatment), 20 with gestational hypertension (GHTN), and 30 controls were enrolled. Of the women with CHTN who had antihypertensive therapy, twelve used only labetalol, and two had labetalol combined with either hydralazine/furosemide or nifedipine. The other two women received metoprolol for blood pressure control.

Seven patients (23%) with CHTN (5 with and 2 without medication), 3 (10%) of the control group and 5 (25%) patients with GHTN later developed PE.

Maternal demographics were similar for both groups, except for gestational age at examination and delivery, pre-gestational BMI and parity *(table 1)*.

Women with PE/SiPE (ARI 5.5 ± 1.6) or CHTN (ARI 5.6 ± 1.7) had a significantly lower ARI than the control group (ARI 6.7 ± 0.8), while GHTN (ARI 6.7 ± 0.8) was not associated with an altered ARI *(Figure 1, table 2)*. There was no difference in ARI between women with CHTN with and without medication (ARI = 5.4 ± 1.9 vs. 5.8 ± 1.4, P=0.55). These outcomes did not change after adjusting for pre-pregnancy BMI and gestational age at the time of study.

| | PE (n=30) | CHTN (n=30) | GHTN (n=20) | Control (n=30) | P-value (ANOVA) |
|---|---|---|---|---|---|
| **Maternal age (years)** | 30 ± 7 | 29 ± 6 | 31 ± 5 | 30 ± 6 | 0.83 |
| **Pre-gestational BMI (kg/m²)** | 29 ± 8 | **36 ± 9*** | 31 ± 8 | 31 ± 5 | **<0.001** |
| **Diabetes Mellitus Type 2 Gestational** | 6 (20%)<br>2 (7%)<br>4 (13%) | 6(20%)<br>2 (7%)<br>4 (13%) | 2 (10%)<br>0<br>2 (10%) | 0 | 0.061 |
| **Twin pregnancy** | 5 (17%) | 0 | 3 (15%) | 2 (7%) | 0.11 |
| **Nulliparous** | **23 (77%)†** | 11 (37%) | 12 (60%) | 17 (57%) | **0.020** |
| **EGA at study (week$^{day}$)** | $35^{4}$<br>($24^{1}$ – $40^{1}$) | **$33^{4}$**<br>**($20^{0}$ – $38^{2}$)†** | $37^{1}$<br>($27^{6}$ – $38^{6}$) | $36^{0}$<br>($23^{3}$ - $40^{3}$) | **0.002** |
| **EGA at delivery (week$^{day}$)** | **$35^{6}$**<br>**($24^{3}$ – $40^{2}$)†** | **$37^{2}$**<br>**($24^{4}$ – $39^{1}$)†** | **$38^{0}$**<br>**($28^{6}$ – $39^{0}$)†** | $39^{1}$<br>($33^{4}$ – $41^{0}$) | **<0.001** |

***Table 1) Demographic data.*** *EGA: Estimated gestational age; PE: preeclampsia; CHTN: Chronic hypertension; GHTN: gestational hypertension; BMI: Body mass index. Data are mean ± SD, median (range) or number (%)*
*Indicated P-values by ANOVA, ANOVA on ranks or Chi-square. *P < 0.001 vs. control (ANOVA with Bonferroni test); †P < 0.05 vs. control (ANOVA on Ranks with Dunn's test)*

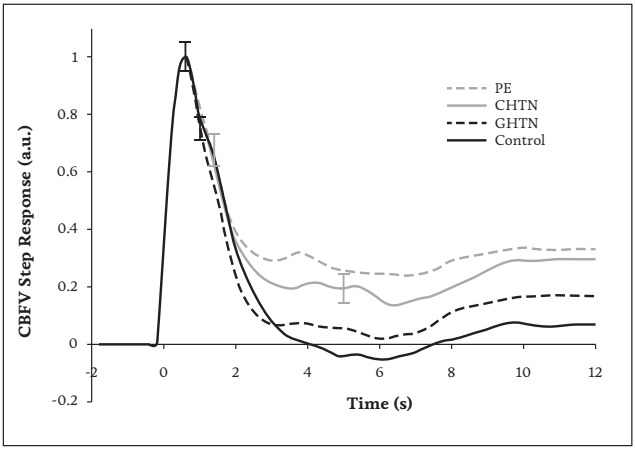


***Figure 1)*** *Average cerebral blood flow velocity (CBFV) step responses of all groups.*
*PE: Preeclampsia; CHTN: Chronic hypertension; GHTN: gestational hypertension; a.u. arbitrary unit.*
*Error bars represent largest ± standard error of the mean.*

The ARI of women with SiPE was significantly lower than in those with new onset PE (3.9 ± 2.2 vs. 6.0 ± 1.1, P=0.002, *Figure 2*), but the ARI in new onset PE was still decreased when compared to the control group (6.0 ± 1.1 vs. 6.7 ± 0.8, P=0.007). RAP was significantly higher in PE and GHTN than in the controls, and even higher in the patients with SiPE. CrCP was lower in GHTN than in controls, but although there was a trend to a lower CrCP in PE, this difference did not reach significance.

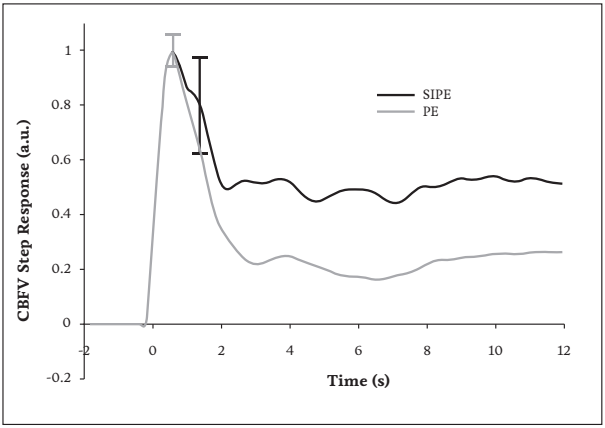


***Figure 2)*** *Average cerebral blood flow velocity (CBFV) step responses of the preeclampsia group subdivided into superimposed PE (SiPE) and preeclampsia (PE). a.u. arbitrary unit. Error bars represent largest ± standard error of the mean.*

ARI, RAP and CrCP were not significantly associated with MAP in women with preeclampsia. However, in both CHTN and control pregnant women, BP was positively associated with RAP (resp. P<0.0001 and P=0.014 respectively). Women with GHTN demonstrated a MAP positive association with CrCP and ARI (P=0.026 and P=0.037).

In subgroup analysis of women who did or did not develop preeclampsia (Table 2), the ARI was significantly lower in women with CHTN who subsequently developed SiPE versus those that did not. This was not seen in the GHTN group or controls. The time between the measurements and the development of PE varied widely, but was not different between the three groups. *(Table 2)*

| | **PE (n=30)** *New PE (23) SiPE (7)* | **CHTN (n=30)** *No later PE (23) Later PE (7)* | **GHTN (n=20)** *No later PE (15) Later PE (5)* | **Control (n=30)** *No later PE (27) Later PE (3)* | **P-value** |
|---|---|---|---|---|---|
| **ARI** | **5.5 ± 1.6**†<br>6.0 ± 1.1<br>**3.9 ± 2.2**¶ | **5.6 ± 1.7**†<br>6.1 ± 1.2<br>**3.9 ± 1.9**¶ | 6.7 ± 0.8<br>6.7 ± 1.0<br>6.9 ± 0.3 | 6.7 ± 0.8<br>6.6 ± 0.8<br>7.2 ± 0.3 | **<0.001** |
| **MAP (mmHg)** | **103 ± 13**‡<br>101 ± 12<br>111 ± 14 | **94 ± 12**‡<br>92 ± 12<br>100 ± 11 | **100 ± 11**‡<br>98 ± 11<br>107 ± 6 | 83 ± 10<br>82 ± 10<br>91 ± 10 | **<0.001** |
| **$EtCO_2$ (mmHg)** | 33 ± 2<br>33 ± 2<br>34 ± 2 | 33 ± 2<br>33 ± 2<br>33 ± 3 | 34 ± 1<br>34 ± 1<br>**33 ± 1**‖ | 33 ± 2<br>33 ± 2<br>34 ± 0.3 | 0.40 |
| **Mean CBFV (cm/s)** | **86 ± 32**‡<br>78 ± 16<br>**113 ± 55**¶ | 69 ± 11<br>68 ± 11<br>71 ± 11 | 68 ± 11<br>68 ± 12<br>71 ± 6 | 68 ± 9<br>67 ± 9<br>76 ± 5 | **<0.001** |
| **CrCP (mmHg)** | 5 ( 0 – 40)<br>9 (0 – 40)<br>1 (0 – 34) | 14 (0 – 35)<br>15 (0 – 35)<br>7 (0 – 33) | **7 (0 – 34)**§<br>7 (0 – 34)<br>10 (2 – 14) | 16 (0 – 26)<br>15 (0 – 26)<br>21 (12 – 23) | **0.012** |
| **RAP ($mmHg.s.cm^{-1}$)** | **1.29 ± 0.37***<br>1.21 ± 0.33<br>**1.55 ± 0.41**‖ | 1.17 ± 0.36<br>1.13 ± 0.35<br>1.28 ± 0.40 | **1.39 ± 0.25**†<br>1.37 ± 0.28<br>1.42 ± 0.08 | 1.05 ± 0.22<br>1.06 ± 0.23<br>0.96 ± 0.20 | **0.001** |
| **Time study to PE diagnosis (days)** | | 15 (4 – 108) | 5 (2 – 14) | 35 (10 -78) | 0.12 |

***Table 2)*** *Hemodynamic data) PE: preeclampsia; SiPE: Superimposed preeclampsia; CHTN: Chronic hypertension; GHTN: gestational hypertension; ARI: autoregulation index; MAP: Mean arterial pressure; $EtCO_2$: End-tidal $CO_2$; CBFV: Cerebral blood flow velocity; CrCP: Critical closing pressure; RAP: Resistance area product. Data are mean ± SD, or median (range)*
*Indicated P-values by ANOVA or ANOVA on ranks. Adjusted P value is adjusted for BMI and gestational age at measurement. *P < 0.05; †P < 0.01 and ‡P ≤ 0.001 vs. control (ANOVA with Bonferroni test); §P < 0.05 (ANOVA on Ranks with Dunn's test); ‖P < 0.05; and ¶P <0.01 vs. new PE or no later PE (t-test or Mann-Whitney U test)*

## 6.4 Comment

In this study, we examined the autoregulation functionality in different hypertensive states of pregnancy, and compared them with those seen in pregnant normotensive controls. Our findings indicate that cerebral autoregulation is impaired in pregnant women with chronic hypertension and preeclampsia, and even more so in patients

with superimposed preeclampsia. Cerebral autoregulation is, however, independent from the actual blood pressure values. Furthermore, the functionality of autoregulation is impaired in pregnant women with chronic hypertension, who subsequently developed superimposed preeclampsia when compared to women who did not develop SiPE. These results may explain why women with CHTN or PE have an increased risk of developing cerebral complications or stroke during pregnancy, even without sudden or excessive elevation in blood pressure.[11-13]

Previous studies also have shown abnormal cerebral hemodynamics in PE, SiPE and CHTN,[6, 21-23] and interpreted the finding of increased cerebral perfusion pressure (CPP) or CBFV as impaired autoregulation. However, none of these measured CBFV and BP simultaneously, and therefore could not assess the dynamic cerebral autoregulation. More recently, our group demonstrated decreased autoregulation index (ARI) in women with preeclampsia when compared to normotensive controls,[5] with the largest degree of impairment in women with SiPE who required ≥ 2 antihypertensive drugs to control their BP. In this study, we also found a significant difference between SiPE and new onset PE. Indeed, the ARI of patients with new onset PE was not much different from the ARI of CHTN (5.9 ± 1.3 vs 5.6 ± 1.7, P=0.48). But in both groups, the large range in ARI indicates non-homogeneity in disease severity and possibly pathophysiology. In addition, women with CHTN who subsequently developed SiPE had a significantly lower ARI than those who did not progress to this disease, while the ARI in the GHTN and control groups were similar for those who did and did not progress to preeclampsia.

The spectrum of conditions, ranging from SiPE, PE and CHTN to GHTN and controls, along with their associated spectrum in ARI, might reflect a range of endothelial impairment. Scientific evidence suggests that altered expression of angiogenic factors produce systemic endothelial dysfunction and play an important role in the pathogenesis of preeclampsia.[14] The extent of these deviations depends on the type of hypertensive disorder, being more pronounced in PE than in CHTN and GHTN when compared to controls.[24-26] Another study found an altered angiogenic balance in PE, but not in GHTN.[27]

These results are in agreement with our study. We also found that the ARI was lowest in the PE group, while the ARI in GHTN was similar to the control group. The proteinuria seen in PE is caused by renal endothelial dysfunction and is also related to this angiogenic inbalance.[14]

The increase in RAP seen in GHTN and PE is in accordance with a previous study, suggesting that RAP might reflect myogenic activity.[28] Interestingly, CrCP, which is more indicative of metabolic control,[28] appears to be decreased in both PE and GHTN, counteracting the effect of RAP. This suggests an abnormal neurovascular coupling, which was also seen in former (pre)eclamptic women.[29] Further work is required to establish the interpretation and significance of this difference.

Women with CHTN who subsequently did develop SiPE had a significantly decreased ARI. Their ARI was comparable to patients who already had SiPE. This can be explained in two possible ways. First, it is possible that the changes in cerebral autoregulation occur before clinical symptoms of SiPE appear, reflecting early manifestation of disease or the underlying pathophysiology. This possibility is further supported by the finding that CHTN outside of pregnancy does not appear to alter cerebral autoregulation, even in sustained untreated middle-aged and older people.[30-32] Furthermore, previous research has demonstrated that decreased maternal MCA resistance in the second trimester was predictive of subsequent preeclampsia in low-risk pregnant women, who can be expected to have no endothelial dysfunction at the time of the TCD examination.[33] These findings, coupled with evidence that angiogenic factors have been detected in maternal serum 5 to 10 weeks before the onset of preeclampsia, suggest that ARI may indeed be impaired in these cases well before the clinical manifestation of disease.[14, 24, 27] If this is in fact true, the ARI could have the potential of being used as a screening tool.

A second hypothesis is that the reduced ARI is an indication of baseline endothelial dysfunction, making pregnant women with CHTN more susceptible for developing SiPE. This is supported by the fact that women with CHTN or diabetes develop PE at a lower level of angiogenic disturbance,[25] and would also explain why the ARI in women with GHTN and controls was normal. In CHTN, endothelial

function is already impaired, and the angiogenic imbalance causes a second hit and SiPE. This theory is in agreement with Noori *et al.*, who found impaired endothelial function in the brachial artery before angiogenic factors were altered.[27]

One of the strengths of this study is the inclusion of patients with multiple hypertensive disorders of pregnancy and a pregnant control group, who were all studied in an identical setting. Further, none of the women received magnesium sulfate or had recent changes in antihypertensive therapy at time of the measurement.

This study also has some limitations, which merit discussion. A limitation of using TCD is that only the cerebral blood flow velocity (CBFV) can be obtained, and therefore relies on the assumption that changes in CBFV are directly proportional to changes in CBF. The data only represent a 7-minute period. While the reliability of the method has been proved in a longitudinal fashion in non-pregnant subjects, this might not hold true for preeclampsia, where blood pressures can be very labile. The study has a small sample size, predominantly in the SiPE, and GHTN groups, and in the comparison of those who did versus those who did not develop PE later during their pregnancy, which precluded any detailed subgroup analysis on severity of preeclampsia, laboratory abnormalities or neurological symptoms. The incidence and severity of adverse events in CHTN is related to the duration of the disease and the severity and control of the hypertension,[7] but we do not have information on this from our patients. Finally, the women with chronic hypertension had a significant higher pre-gestational BMI and were studied at a younger gestational age, but controlling for this possible confounder in a multiple regression analysis did not change the results.

In conclusion, our findings suggest the presence of impaired dynamic cerebral autoregulation in patients with PE, particularly in those with SiPE, when compared to their GHTN or normotensive counterparts. The autoregulation is impaired in patients with CHTN who subsequently develop SiPE, but not in normotensive pregnant women or women with GHTN who subsequently develop PE. Whether this disparity is due to preexistent differences or early affected cerebral circulation in pregnant women with CHTN remains to be determined.

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# CHAPTER 7

## CEREBRAL AUTOREGULATION IN PREGNANCIES COMPLICATED BY DIABETES AND OVERWEIGHT

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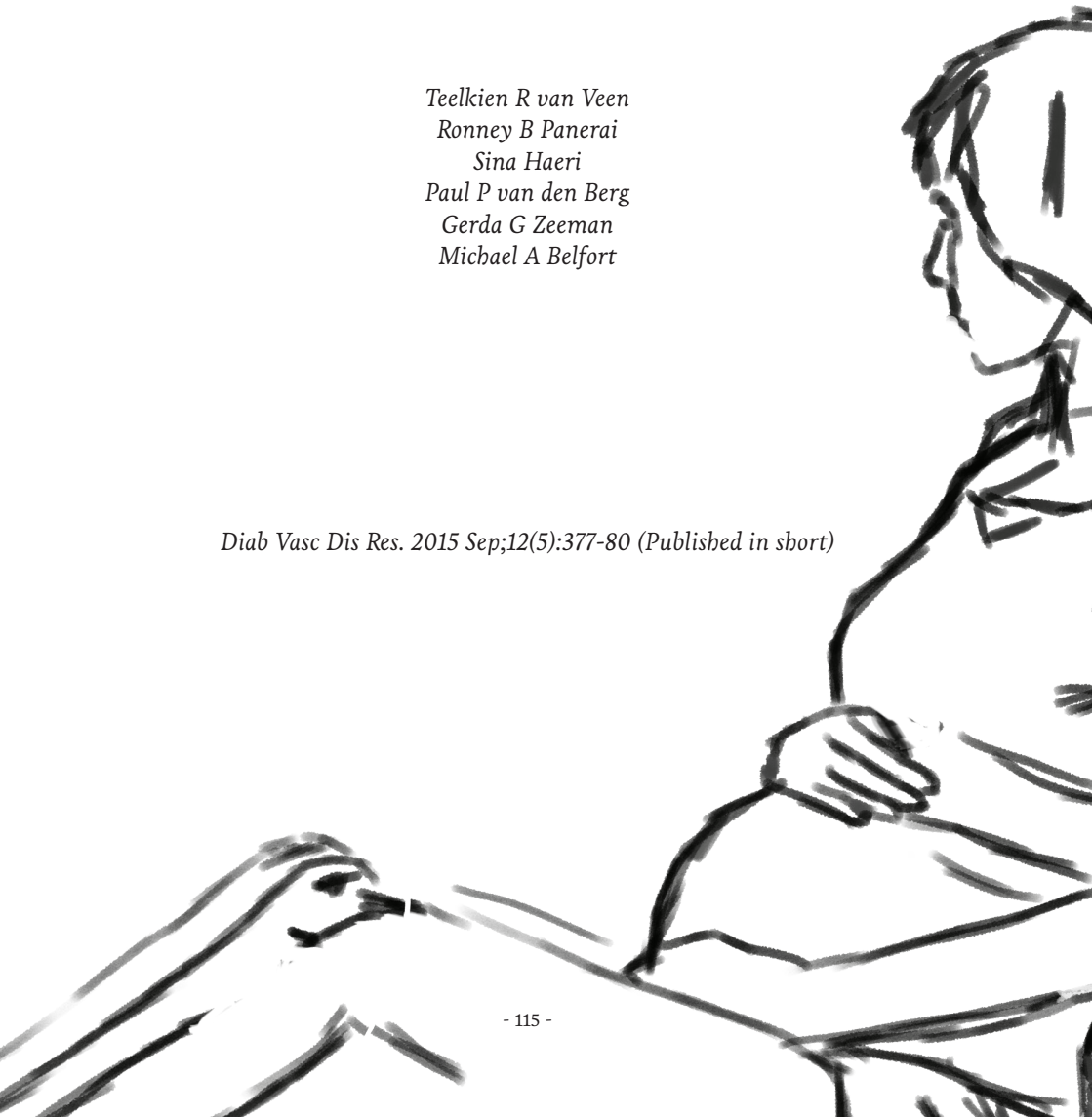

## Abstract

***Aim:*** *The aim of this study was to estimate the impact of diabetes and obesity on cerebral autoregulation in pregnancy.*

***Methods:*** *Cerebral autoregulation was evaluated in women with gestational diabetes (GDM), type 2 diabetes (DM2), and/or overweight (body mass index (BMI ≥ 25 kg.m$^{-2}$), and compared to a cohort of euglycaemic pregnant women. The autoregulation index (ARI) was calculated using simultaneously recorded cerebral blood flow velocity in the middle cerebral artery and blood pressure. ARI values of 0 and 9 indicate absent and perfect autoregulation, respectively.*

***Results:*** *ARI in women with either diabetes (n = 33, 6.6 ± 1.1), or overweight (n = 21, 6.7 ± 0.6), was not significantly different to that in control patients (n = 23, 6.6 ± 0.8, P = 0.96).*

***Conclusions:*** *Cerebral autoregulation is not impaired in pregnant women who have non-vasculopathic diabetes or overweight. This suggests that the increased risk of preeclampsia in diabetic and overweight women is not associated with early impaired cerebral autoregulation.*

## 7.1 Introduction

Preeclampsia (PE) is a multisystem disease, which complicates 2-8% of pregnancies.[1] The exact pathogenesis is still unknown, but maternal obesity and insulin resistance are believed to be important contributing factors.[2] While the risk of PE is increased with pre-gestational diabetes,[3] the association between PE and gestational diabetes (GDM) is less pronounced, and studies are conflicting.[4, 5] This inconsistency is likely to be due to heterogeneity of the GDM population, with regard to the degree of impaired glucose metabolism, glycaemic control, and its time of onset during pregnancy. Further confounding the association is that women with GDM often have co-existing obesity, which in itself is an independent risk factor for preeclampsia.[6, 7]

Patients with diabetes have increased cardiovascular complications, including stroke. These complications could arise due to endothelial dysfunction, which is common in early and otherwise uncomplicated type II diabetes (DM2).[8]

Preeclampsia is associated with altered cerebral hemodynamics,[9, 10] and represents a risk factor for cerebrovascular complications.[11, 12] Impaired cerebral autoregulation may explain the development of cerebral oedema, convulsions, or cerebral haemorrhage, even in the absence of significant hypertension.[13, 14]

Cerebral autoregulation is a physiological process that maintains blood flow at an appropriate level despite changes in blood pressure. Studies on cerebral autoregulation in non-pregnant patients with DM2 have shown conflicting results, showing either impaired autoregulation[15, 16] or no difference[17, 18] compared with control subjects. Differences in disease duration, severity and complications may underlie these inconsistencies. Preliminary evidence indicates impaired cerebral autoregulation in PE when compared to normotensive controls.[9]

The effect of diabetes in pregnancy on the autoregulatory capacity is not known. Based on the increased risks of preeclampsia and cerebrovascular complications in patients with pre-gestational diabetes, but a less pronounced relationship with GDM, we hypothesize that the cerebral autoregulation is impaired in DM2, but not in GDM. Consequently, the primary aim of this study was to estimate

the impact of diabetes and obesity on cerebral autoregulation in pregnancy.

## 7.2 Materials and Methods

We conducted a prospective cohort study in non-labouring pregnant women without a history of cerebrovascular disease, and with an estimated gestational age (EGA) >20 weeks. Cases included women with gestational diabetes (GDM), type 2 diabetes (DM2) (cases), or overweight (prepregnancy body mass index (ppBMI ≥ 25 $kg.m^{-2}$) who were otherwise healthy. The referent population included healthy normotensive pregnant women with a ppBMI < 25. All women were screened for glucose intolerance using the 1-hour 50 gr. glucose challenge. Study participants were recruited from the outpatient clinics at Texas Children's Pavilion for Women in Houston and North Austin Maternal-Fetal Medicine in Austin, Texas during a routine prenatal care visit. One experienced examiner (TRVV) performed all of the measurements. The study was approved by the local Institutional Review Boards at Baylor College of Medicine in Houston, Texas and North Austin Medical Center in Austin, Texas, and informed written consent was obtained from each participant prior to data collection.

Inclusion criteria comprised pregnancy and maternal age greater than 18 years. Women were excluded if they had chronic medical illnesses (other than diabetes), used antihypertensive medications, smoked, used illicit drugs, or if they developed preeclampsia during their pregnancy. Furthermore, in the control and study groups, we excluded anyone who developed gestational diabetes after enrolment. Women with diabetes were excluded if they had underlying proliferative vasculopathy (White's classification D or higher). GDM was diagnosed according to ACOG guidelines.[19] GDM patients were categorized into A1 (diet controlled), and A2 (medication controlled). Women diagnosed with diabetes prior to 16 weeks of gestation were classified as "pre-gestational."

Data from both the medical record and from patient interview were entered into a standardized database (Access, Microsoft Corp. Seattle, WA). The following maternal characteristics were based on self-report: race/ethnicity, height, pre-pregnancy weight, smoking

and alcohol and illicit substance use. Gestational age (EGA) was determined by menstrual dating. In cases of uncertain menstrual dates, first trimester ultrasound estimates of EGA were used.

Cerebral autoregulation was assessed by using a combination of transcranial Doppler (TCD) and continuous non-invasive blood pressure measurement,[20] and is expressed as the Autoregulation Index (ARI), with 0 being absent and 9 perfect cerebral autoregulation.[21]

At the time of the TCD examination, brachial systolic (SBP) and diastolic (DBP) blood pressure were measured. Patients were studied in a semi-Fowlers position in a private room. Simultaneous transcranial Doppler (TCD) evaluation of both middle cerebral arteries (MCA) was carried out using two 2 MHz pulsed, range gated probes (Spencer Technologies, Seattle, WA), held in place using a head frame. If only one MCA could be found, that one side was used in the analysis.

Blood pressure was continuously measured non-invasively using finger arterial volume clamping (Finometer Pro, Finapres Medical Systems, Amsterdam, The Netherlands) with the servo-adjust switched off, after an acclimatization period of at least 5 minutes, when a stable waveform was achieved with the servo-adjust on. This was subsequently calibrated with the brachial BP. The BP tracing also served to mark each cardiac cycle. End-tidal $CO_2$ ($EtCO_2$) was measured with a nasal cannula (Nellcor Oximax N-85, Covidien, Mansfield, MA).

All data were recorded at 50 Hz, interpolated to 200 Hz and visually inspected during analysis to remove occasional large spikes. A median filter was used to remove small spikes and artefacts in the cerebral blood flow velocity CBFV signal. All signals were then low-pass filtered with a Butterworth filter with a cut-off frequency of 20 Hz. Mean BP, bilateral CBFV, $EtCO_2$ and heart rate were then calculated for each beat. The critical closing pressure (CrCP) and resistance-area product (RAP) were obtained using the first harmonic of BP and CBFV of each cardiac cycle (24). All beat-to-beat time series of parameters were then interpolated with a 3$^{rd}$ order polynomial and resampled at 5 Hz.

Cerebral autoregulation was determined from the CBFV responses to spontaneous fluctuations in mean arterial BP as described previously.[22] Auto- and cross-spectral estimates were obtained with

the fast Fourier transform (FFT), using data segments of 512 samples and 50% superposition (Welch method), to obtain the transfer function parameters coherence, gain and phase in the low frequency range (<0.1 Hz). The inverse FFT was then performed to estimate the impulse and step responses. The CBFV step response to a sudden change in ABP was compared to 10 template curves proposed by Tiecks *et al*.[21] and the best fit curve corresponded to the ARI autoregulation index.[21, 22] Measurements were rejected if coherence did not reach 0.5 for any frequency <0.25 Hz.

Baseline cerebral hemodynamic parameters are reported as the average over a 7 minute baseline recording.

All data sets were checked for normalcy of distribution (Kolmogorov-Smirnov test). Data are reported as mean and standard deviation, or median and [range] as appropriate. Analyses were performed using ANOVA with Bonferroni's post-hoc test or ANOVA on Ranks with Dunn's post hoc test (both comparisons versus the control group). (Sigmastat 2004, Systat Software, Richmond, CA). $P < 0.05$ was used to indicate statistical significance.

## 7.3 Results:

A total of 36 women with DM (GDMA1, GDMA2, and DM2, 12 in each group), 24 overweight women without DM ( ppBMI > 25 $kg.m^{-2}$), and 24 control women (ppBMI<25 $kg.m^{-2}$) were enrolled.

One woman with GDMA1, 2 with DM2, 3 with overweight/obesity and 1 women in the control group later developed PE and were excluded from the analysis.

Maternal demographics were similar for both groups, except for BMI and gestational age at delivery *(Table 1)*. Patients with DM2 used either insulin (n=4), Glyburide (n=4), both insulin and Glyburide (n=1) or metformin (n=1) for glucose control. All patients with GDMA2 used Glyburide.

When compared with the control group, women with GDM, DM2, and high BMI did not have any significant ARI differences. There was also no difference noted between GDMA1, GDMA2 and DM2 (ARI 6.5 ± 1.5, 6.4 ± 1.0 and 6.9 ± 0.6, P=0.53). CBFV was lower in patients with DM2, however, this was not clinical significant. None of the other parameters in Table 2 were different between these three

| | Diabetes Mellitus (n=33) | Overweight (BMI≥25) (n=21) | Control (BMI<25) (n=23) | p (ANOVA) |
|---|---|---|---|---|
| **Maternal age (years)** | 30 ± 6 | 29 ± 5 | 30 ± 7 | 0.74 |
| **Prepregnancy BMI (kg.m$^2$)** | **30.8 (20.0-58.6)**† | **29.9 (25.1-39.2)**† | 22.6 (18.2-24.5) | **<0.001** |
| **EGA at study (week$^{day}$)** | $34^6$ ($24^5$-$38^3$) | $33^6$ ($20^3$-$40^3$) | $35^5$ ($24^4$-$40^2$) | 0.74 |
| **Twin pregnancy** | 0 | 2 (10%) | 1 (4%) | 0.11 |
| **EGA at delivery (week$^{day}$)** | **$38^0$ ($27^3$-$41^0$)** † | $39^0$ ($32^0$-$41^0$) | $39^1$ ($28^0$-$41^1$) | **0.020** |
| **Birth weight (grams)** | 3280 ± 551 | 3157 ± 613 | 3072 ± 698 | 0.47 |

***Table 1) Demographic data.*** *EGA: Estimated gestational age; BMI: Body mass index. Data are mean ± SD, median (range) or number (%) Indicated P-values by ANOVA, ANOVA on ranks or Chi-square†P < 0.05 vs. control (ANOVA on Ranks with Dunn's test)*

| | Diabetes Mellitus (n=33) | Overweight (BMI>25) (n=21) | Control (BMI<25) (n=23) | P –value (ANOVA) |
|---|---|---|---|---|
| **ARI** | 6.6 ± 1.1 | 6.7 ± 0.6 | 6.6 ± 0.8 | 0.88 |
| **Phase (rads)** | 1.27 ± 0.29 | 1.25 ± 0.29 | 1.27 ± 0.27 | 0.96 |
| **Coherence** | 0.39 ± 0.10 | 0.39 ± 0.11 | 0.44 ± 0.11 | 0.107 |
| **Gain (cm.s$^{-1}$. mmHg$^{-1}$)** | 0.69 ± 0.21 | 0.67 ± 0.21 | 0.78 ± 0.29 | 0.26 |
| **CBFV (cm.s$^{-1}$)** | 61 ± 8 | 68 ± 8 | 64 ± 10 | **0.032** |
| **MAP (mmHg)** | 86 ± 11 | 82 ± 9 | 80 ± 10 | 0.062 |
| **$EtCO_2$ (mmHg)** | 33 ± 2 | 33 ± 2 | 34 ± 2 | 0.14 |
| **CrCP (mmHg)** | 11.2 (0-30) | 10.5 (0-32) | 14.6 (0-31) | 0.77 |
| **RAP (mmHg.s.cm$^{-1}$)** | 1.2 (0.8-1.8) | 1.2 (0.9-3.0) | 1.1 (0.6-1.8) | 0.11 |

***Table 2) Hemodynamic data.*** *ARI: autoregulation index; CBFV: Cerebral blood flow velocity; MAP: Mean arterial pressure; $EtCO_2$: End-tidal $CO_2$; CrCP: Critical closing pressure; RAP: Resistance area product. Phase, coherence and gain are obtained in the low frequency range (<0.1 Hz). Data are mean ± SD, or median (range). Indicated P-values by ANOVA or ANOVA on ranks.*

groups. Patients who later developed preeclampsia and who were excluded had an average ARI of 6.2 ± 1.5 (range 4.2 – 7.8), which was not significantly different from the control group (P=0.34) However, the study was not powered to find this difference.

## 7.4 Discussion

In this study, dynamic autoregulation in pregnancies complicated by diabetes was examined and compared to normotensive and euglycaemic pregnant controls with BMI < 25 kg.m$^{-2}$. The findings indicate that cerebral autoregulation is not impaired in women with (uncomplicated non-vasculopathic) diabetes in pregnancy. Furthermore, the functionality of autoregulation is equally effective in euglycaemic women with and without pre-pregnancy obesity.

GDM,[23] DM2,[8, 24] and obesity[8, 25] all are associated with endothelial dysfunction and chronic inflammation. These abnormalities lead to atherosclerosis and contribute to the increased cerebrovascular mortality and morbidity seen in DM2 and obesity.[24] A study on cerebral infarction in young adults found an odds ratio of 11.6 for diabetes.[26]

The effect of diabetes and subsequent endothelial dysfunction on cerebral autoregulation is less clear. Two studies in non-pregnant DM2 patients with good glycaemic control and no major complications showed normal autoregulation.[17, 18] Others found affected dynamic autoregulation in DM2 with,[15] and without[15, 16] microvascular disease. We did not find evidence suggesting affected dynamic cerebral autoregulation in our group of pregnant women with DM2, but comparison with the aforementioned studies is difficult due to differences in age, disease duration and severity, and gender. None of our patients had microvascular complications or autonomic neuropathy, which are thought to be associated with cerebral autoregulation impairment in DM.[18, 27] In pregnancy, these factors (characterized by baseline proteinuria and the White classification) are associated with the development of PE.[3] None of the women in the current study had baseline proteinuria or class D diabetes or higher which might explain the lack of impaired autoregulation. Furthermore, interpretation of previous studies on GDM and adverse pregnancy outcomes has been complicated by the fact that these studies were

not differentiated according to disease severity. We studied both diet- and medication controlled GDM separately, but did not find a difference in autoregulation in either of these sub groups. As in the patients with DM2 in our study, we hypothesize that the excellent glycemic control (as shown by daily glucose monitoring), relatively mild hyperglycaemia and short disease duration allow for preserved cerebral autoregulation.

Another explanation for the absence of impaired autoregulation in the current study might be pregnancy in and of itself. The ARI found in all groups seems to be in the high normal range when compared to non-pregnant subjects.[28] This might be the result of the relative hypocapnia seen in pregnancy which improves the autoregulatory capacity,[28] and the hormonal changes of pregnancy which enhance endothelial function.[29]

One of the strengths of this study is the inclusion of both women with diabetes and two groups of women without diabetes (ppBMI < and > 25 kg/m$^2$). Interpretation of the effect of GDM in pregnancy is complicated because these women are often obese, a condition known to be associated with insulin resistance, endothelial dysfunction, a pro-inflammatory state, and preeclampsia.[6, 7, 30]

This study has some limitations, which merit discussion. The incidence and severity of endothelial dysfunction in DM is related to the duration of the disease and the glycaemic control. Although the duration of diabetes differed amongst the patients, none demonstrated poorly controlled diabetes, as determined by their Maternal-Fetal Medicine specialist. However, glycosylated haemoglobin (HbA1c) is not routinely measured in such pregnant patients, and thus was not available to monitor glycaemic control. Patients with diabetic complications (vasculopathy) were excluded from our study, and clearly may have demonstrated a different response given the nature of the disease. Furthermore, we only studied autoregulation within the context of spontaneous fluctuations in blood pressure during rest, which is a mainly myogenic activity. Therefore, we cannot exclude the possibility of CBF changes induced by metabolic activity such as might be present in patients with impaired $CO_2$ cerebrovascular reactivity.[17] Lastly, the women were studied at a wide range of gestational age, but with a comparable median gestational age. The effect of advancing

gestational age on ARI is not known, however, we did not find a correlation between gestational age and ARI (data not shown).

In conclusion, our findings suggest the presence of normal functioning dynamic cerebral autoregulation in normal weight and high BMI pregnant women with pre-gestational and gestational diabetes. This suggests that if such women are at an increased risk for preeclampsia based on their diabetic and/or high BMI status, it is unlikely to be associated with significant impairment in dynamic cerebral autoregulation prior to the development of the hypertensive state. Whether this holds true for patients with advanced diabetic complications remains to be determined by future studies.

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# CHAPTER 8

## LOW MATERNAL MIDDLE CEREBRAL ARTERY DOPPLER RESISTANCE INDICES CAN PREDICT FUTURE DEVELOPMENT OF PREECLAMPSIA

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## Abstract

**Objective:** *To determine if decreased resistance (vasodilatation) in the maternal middle cerebral artery (MCA) in the second trimester can predict third-trimester development of preeclampsia.*

***Methods:*** *Four-hundred and five low-risk gravidas had MCA transcranial Doppler (TCD) once in the second trimester. Maternal/neonatal outcomes were evaluated after delivery. Mean blood pressure, MCA velocities, resistance index (RI), pulsatility index (PI) and cerebral perfusion pressure (CPP) were compared between normotensive and preeclamptic cohorts.*

***Results:*** *Seven subjects (1.7%) developed preeclampsia. An RI of < 0.54 and a PI of < 0.81 were clinically useful in predicting subsequent preeclampsia. Areas under the receiver–operating characteristics curves for RI and PI were 0.93 and 0.93, respectively, with optimal sensitivity and specificity of 86% and 93% for both variables. Positive and negative likelihood ratios were 11.8/0.15 (RI) and 12.3/0.15 (PI).*

***Conclusion:*** *TCD indices of low maternal MCA resistance in the second trimester are predictive of the subsequent development of preeclampsia in a low-risk, ethnically homogeneous population.*

## 8.1 Introduction

Hypertensive disorders are a major contributor to maternal mortality worldwide.[1, 2] The incidence of all hypertensive disorders in pregnancy may be as high as 17% in nulliparous women, with the incidence of preeclampsia reportedly between 2 and 7%.[3]

Although the etiology of preeclampsia remains unclear, current thought is that it follows from the failure of second-wave trophoblastic invasion in the late first and early second trimesters.[4-8] As a result of the failed replacement of the spiral artery muscularis, these arteries do not transform into low-resistance conduits and uteroplacental resistance fails to decrease. In order to improve placental perfusion, it may be hypothesized that there is compensatory production of vasodilator substances by the placenta. These circulating factors, as a secondary effect, dilate vessels in multiple organs, including aorta, myometrium and mesentery.[4-6, 8] Easterling *et al*.[9] and others[10, 11] have reported increased cardiac output in the second and early third trimesters, consistent with the presence of circulating vasodilator and inotropic substances.

Transcranial Doppler (TCD) ultrasound[12-14] and velocity-encoded phase-contrast magnetic resonance imaging (MRI)[9] have been used to study cerebral hemodynamics in normal pregnancy as well as in women with preeclampsia, and normative data for pregnancy have been published.[13-16] Riskin-Mashiah *et al*.[17] showed that women destined to develop preeclampsia had lower middle cerebral artery (MCA) resistance index (RI) and pulsatility index (PI) weeks before the development of preeclampsia.[17] In that study, TCD ultrasound was used in the late second and early third trimesters (19–28 weeks).[17] In the current study we aimed to further research the hypothesis that Doppler RI values in the maternal MCA can be used to reliably predict the subsequent development of preeclampsia by using a much larger sample size and by studying patients in the second trimester.

## 8.2 Methods

The protocol was approved by the Institutional Review Board for Human Investigation at St. Mark's Hospital in Salt Lake City, Utah. All patients gave written informed consent. Normal pregnant women undergoing routine second-trimester obstetric ultrasound

examination in a maternal-fetal medicine practice were consecutively recruited for this study over a 4-year time period, from 2005 to 2009. Sample-size calculation on the basis of our previous work evaluating MCA-RI values and on an estimated preeclampsia rate of 5% indicated an enrollment goal of approximately 300 subjects ($\alpha$ = 0.05, ß = 0.20). Limitations in study resources and staff influenced the duration of the enrollment period. Women with chronic illness (including chronic hypertension), fetal anomalies, multiple pregnancy, medications other than vitamins and thyroxine, more than a trace of proteinuria or blood pressure (BP) > 140/90 mmHg at the time of the ultrasound examination were excluded. Gestational age was documented by confirmed last menstrual period and/or first-trimester ultrasound dating.

All patients were sitting upright in a chair in a quiet examination room and did not talk or move during the examination. Measurement of MCA flow velocities was performed by one of three study sonographers trained by the principal investigator. While no interobserver or intraobserver error was calculated specifically for this study, we and others have previously reported that error for MCA measurements is less than 10%.[18-20] A 2-MHz- pulsed, range-gated TCD probe (Nicolet Companion EME; Nicolet Vascular, Madison, WI, USA) was used to insonate the M1 portion (the initial 2-cm segment) of the MCA via the transtemporal approach. The depth of interrogation was adjusted to optimize the Doppler signal. The MCA velocity waveform was recorded on both sides of the head, if possible, and the averaged value was then used in the analysis. In those cases in which the MCA waveform could be obtained from only one side of the head (n=70, 17% of cases) this value was used. A minimum of six waveforms were averaged for each side. The systolic, diastolic and mean velocities of the waveform spectrum were recorded and saved as hard copy. Derived MCA values were calculated as follows:

$PI = (Velocity_{systolic} - Velocity_{diastolic})/Velocity_{mean}$;
$RI = (Velocity_{systolic} - Velocity_{diastolic})/Velocity_{systolic}$;
Cerebral perfusion pressure (CPP) = $(Velocity_{mean}/(Velocity_{mean} - Velocity_{diastolic}) \times (\text{Mean arterial pressure} - BP_{diastolic})$;[18, 19]

Resistance area product (RAP) = Mean arterial pressure/ $Velocity_{mean}$;[21]
Cerebral flow index (CFI) = CPP/RAP;[22]
Critical closing pressure (CCP) = Mean arterial pressure - CPP

At the time of TCD examination, BP was measured at the brachial artery on both arms, and urine was checked for proteinuria using a dipstick. The mean arterial pressure (MAP) was calculated using the following formula: MAP = $(BP_{systolic} + (2 \times BP_{diastolic}))/3$.

Maternal and neonatal outcomes were evaluated after delivery by chart review. Preeclampsia was defined as BP ≥ 140 mmHg systolic and/or > 90 mmHg diastolic, and proteinuria > 1+ on a dipstick (or > 300 mg by 24-h col- lection). BP elevation without proteinuria was considered to be gestational hypertension (GH). Both classifications required new onset of symptoms after 20 weeks of gestation in a woman with previously normal BP.[23]

All data were tested for normality of distribution by visual comparison of the frequency distribution histogram with a superimposed normal curve, as well as by visual evaluation of a Q-Q plot comparing each distribution with the normal distribution. The groups (normotensive, hypertensive and preeclamptic) were compared using appropriate parametric (Student's t-test) and non-parametric (Mann – Whitney U-test) tests. Multiple MCA flow characteristics and derived values were evaluated for their predictive ability by calculating the area under the curve (AUC) of the receiver – operating characteristics (ROC) curve. Multivariable prediction models combining potential predictors of preeclampsia were tested using binary logistic regression. Sensitivity and specificity were calculated, as well as likelihood ratios (LRs) and predictive values. All statistical tests were performed using SPSS 19 (SPSS Inc., Chicago, IL, USA). Data are reported as mean ± SE (or median and range), and statistical significance was set at a probability value of < 0.05.

## 8.3 Results

A total of 405 women met the inclusion criteria and had good-quality TCD waveform measurements. TCD measurements were made at a mean of 19.0 ± 1.3 weeks (range, 12–26 weeks). Seven (1.7%) subjects developed preeclampsia at an average of 37.3 ±

| Characteristic | Normal (n=383) | GH (n=15) | PE (n=7) | Normal vs GH (two-tailed significance) | Normal vs PE (two-tailed significance) |
|---|---|---|---|---|---|
| **Age (years)** | 285 | 26±4 | 29±6 | NS | NS |
| **BMI (kg/m²)** | 25±6 | 29±6 | 27±5 | 0.03 | NS |
| **Caucasian (%)** | 91 | 100 | 100 | NS | NS |
| **Gravidity** | 2 (1–12) | 1 (1–3) | 2 (1–5) | 0.023 | NS |
| **GA at TCD (weeks)** | 19±1.3 | 19±2.2 | 19±1.5 | NS | NS |
| **GA at PE diagnosis (weeks)** | N/A | N/A | 37.3±2.6 | N/A | N/A |
| **Systolic BP (mmHg)** | 110±10 | 120±9 | 115±10 | 0.0003 | NS |
| **Diastolic BP (mmHg)** | 69±7 | 73±7 | 76±8 | 0.046 | NS |
| **MAP (mmHg)** | 82±7 | 89±7 | 89±7 | 0.004 | 0.04 |
| **MCA systolic velocity (cm/s)** | 93±19 | 91±17 | 99±26 | NS | NS |
| **MCA diastolic velocity (cm/s)** | 37±8 | 38±9 | 48±12 | NS | 0.046 |
| **MCA-RI** | 0.60±0.05 | 0.59±0.04 | 0.51±0.05 | NS | 0.02 |
| **MCA-PI** | 1.00±0.15 | 0.95±0.09 | 0.75±0.11 | NS | 0.001 |
| **MCA-CPP** | 40±9 | 47.2±6 | 45±12 | 0.0004 | NS |
| **MCA-RAP** | 1.5±0.4 | 1.6±0.5 | 1.4±0.4 | NS | NS |
| **MCA-CFI** | 27±9 | 31±9 | 36±19 | NS | NS |
| **MCA-CrCP** | 43±11 | 41±10 | 44±14 | NS | NS |

***Table 1)*** *Characteristics at transcranial Doppler (TCD) examination*
*Values are given as percentage, mean ± SD or median (range). BMI, body mass index; BP, blood pressure; CFI, cerebral flow index; CPP, cerebral perfusion pressure; CrCP, critical closing pressure; GA, gestational age; GH, gestational hypertension; MAP, mean arterial pressure; MCA, maternal middle cerebral artery; N/A, not applicable; NS, non-significant; PE, preeclampsia; PI, pulsatility index; RAP, resistance area product; RI, resistance index.*

2.8 weeks' gestation. Demographic data were similar in the women who did and who did not develop preeclampsia *(Table 1)*. All study subjects denied smoking. Most women were Caucasian (91% of the normotensive patients vs 100% of the preeclamptics, P = 0.4). MAP at the time of measurement was higher in the group destined to develop preeclampsia, as was the MCA diastolic velocity. RI and PI values were lower in the group destined to develop preeclampsia. Other measurements and derived values describing cerebrovascular flow and resistance were not significantly different at the time of measurement *(Table 1)*. No correlation was found between RI/PI and arterial BP, maternal age or body mass index (BMI) at the time of measurement. Although RI and PI are known to decrease slightly during pregnancy[24], their correlation with gestational age in this study was very weak (R = 0.03).

MCA-RI and -PI were associated with ROC-AUC values of 0.93 ± 0.04 and 0.93 ± 0.04, respectively, in predicting subsequent preeclampsia *(Figure 1)*, and cut- off values of RI <0.54 and PI <0.81

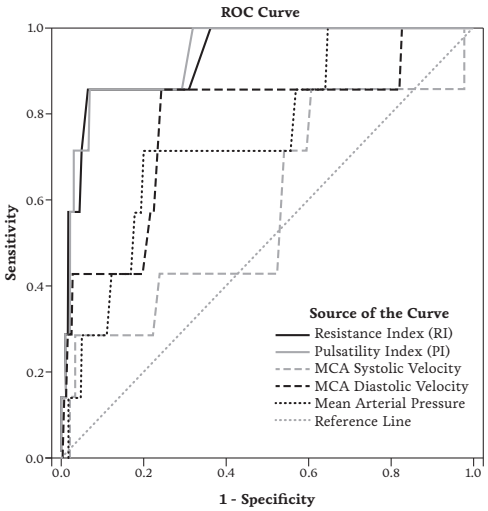


***Figure 1)*** *Receiver–operating characteristics curves showing the performance of second-trimester maternal middle cerebral artery in the prediction of subsequent preeclampsia.*
*Cut-off values of RI <0.54 and PI <0.81 were found to be clinically useful, both with a sensitivity of 86% and specificity of 93%. The diagonal line is the reference line.*

were found to be clinically useful. An RI of <0.54 in the MCA was associated with a positive LR for preeclampsia of 11.8, and a PI of < 0.81 in the same vessel was associated with a positive LR of 12.3. For both RI and PI the negative LR for preeclampsia was low (0.15). Sensitivity and specificity, positive and negative predictive values, and LRs (with 95% CI) are shown in Table 2. No other parameter measured was a strong predictor of preeclampsia and no other parameter contributed independently to any multivariable prediction model. No characteristic or derived index we evaluated was useful to predict GH. The RI/PI values for all study subjects are plotted in *Figure 2*.

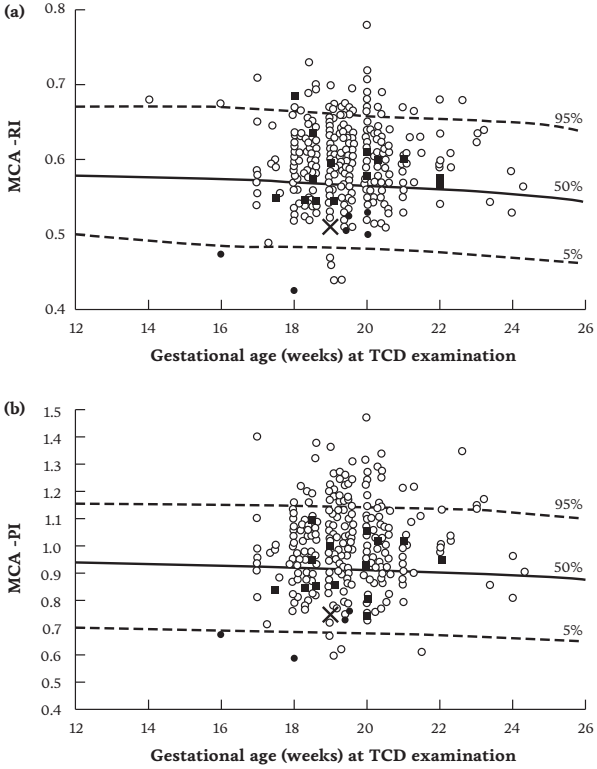


***Figure 2)*** *Scatter plot of second-trimester maternal middle cerebral artery (MCA) resistance index (RI) (a) and pulsatility index (PI) (b) for study subjects who remained normotensive (○) and for those who developed gestational hypertension (■) and preeclampsia (•). The mean value for preeclampsia cases is indicated (X). Normal ranges for RI and PI with median and 5th and 95th percentiles are shown.[24] TCD, transcranial Doppler.*

## 8.4 Discussion

This study suggests that TCD indices of low MCA resistance in the second trimester are predictive of the subsequent development of preeclampsia in a low- risk, ethnically homogeneous population. This supports previous studies showing a reduced RI and/or PI either before[17] or after[13, 14, 16] the clinical development of preeclampsia. The results are also consistent with studies that show preeclampsia to be characterized by a hyperdynamic state with elevated cardiac output and reduced peripheral resistance early in pregnancy.[9-11] Our patients all developed relatively mild and late-onset preeclampsia, and our data support the suggestion of Valensise *et al*.[25] that women likely to develop early-onset preeclampsia (< 34 weeks) show elevated peripheral vascular resistance before the onset of hypertension and proteinuria, while those who will develop preeclampsia late in pregnancy have an initially low vascular resistance.[25] Our results are consistent with this proposal: six of seven preeclamptic patients were diagnosed at or after 34 weeks' gestation.

It has been hypothesized that cerebrovascular autoregulation is altered in overtly preeclamptic women.[7, 12] In one study, low MCA-PI and -RI at a mean of 23 weeks predicted the subsequent development of preeclampsia.[17] However, women who underwent two cerebral autoregulatory challenge tests at the time of examination ($CO_2$ inhalation and hand grip), all showed a normal vasodilatory response.[17] Thus, it is unlikely that these resistance changes early in gestation represent pathologic cerebrovascular dysfunction, but rather more likely that they represent a physiologic compensatory response. This is supportive of the hypothesis that there is release of a circulating vasodilator substance(s) from the placenta before measurable loss of autoregulatory function and/or elevation in BP. In the present study, the mean values of RI (0.51) and PI (0.75) of women who went on to develop preeclampsia were within the normal range[24] but notably low for 19 weeks of gestation *(Figure 2)*. However, estimated CPP for these patients was very near the normal mean for all pregnant women, suggesting intact autoregulation and physiologic compensatory vasodilation. These data underlie the need for further studies to assess cerebrovascular autoregulation before and at the onset of preeclampsia.

In this study, as in our previous study,[17] RI and PI were predictive of preeclampsia but not of gestational hypertension, suggesting that the pathogenesis of gestational hypertension and preeclampsia may differ, at least in the timeline. We have also previously shown that in pregnant women with mild chronic hypertension the baseline PI and RI are similar to those of normotensive pregnant women, despite having a higher baseline mean BP.[26] This finding of normal PI and RI in early pregnancy in hypertensive women who do not go on to develop preeclampsia underlies the contention that the clinical syndrome of preeclampsia is not simply linked to elevated BP, but is more likely to be determined by a separate pathophysiologic pathway.[26]

In our dataset, MCA-RI and -PI were shown to predict preeclampsia better than any previously reported test (86% sensitivity, 93% specificity).[27] Other Doppler- based tests reported to predict preeclampsia at an early gestational age rarely reach specificities above 90% and often require combination with other parameters to exceed 60% sensitivity.[27] We hypothesize that a multivariate model including MCA-RI/PI and other values shown to be predictive of preeclampsia (such as BMI and uterine artery Doppler) may allow further improvement in the detection rate into a reliable, clinically useful, range.

This study was conducted in a low-risk, middle-class, almost exclusively Caucasian population, which limits the ability to generalize the findings across a broader population. A second limiting factor was the low incidence of preeclampsia (1.7%), which reflects the true low regional incidence, predominant ethnic group and socio-economic class represented (confirming that we did not select a mixed risk group or enriched group and that our sample was truly representative of the local population[28, 29]) and the strict definition of preeclampsia we applied (BP ≥ 140 mmHg systolic and/or > 90 mmHg diastolic, and proteinuria > 1+ on a dipstick or > 300 mg by 24-h collection). This low incidence of preeclampsia resulted in wide confidence limits and in a relatively low positive predictive value for preeclampsia using RI and PI (0.17, 0.19, respectively). Additionally, as only one woman developed severe preeclampsia and only one woman developed preeclampsia before 34 weeks of gestation, we could not perform subanalyses of severity and time of development

of the disease. Thus, the preeclamptic and normal groups in our data were not homogeneous, and therefore the within-group variability of hemodynamic values was high. We were also unable to evaluate the predictive ability of the test at specific gestational ages. Clearly, this potential screening test needs to be further developed and tested in a much larger population(s) of ethnically diverse patients at a more uniform gestational age.

The applicability of this test to first-trimester screening is unclear. However, given the low-normal second- trimester RI (< 15%; *Figure 2*) found in those who went on to develop preeclampsia, the hypothesis of abnormal placentation leading to vasodilatation may hold true in the first trimester. It is possible that low MCA- RI in the first trimester has similar predictive capacity. This study is underway, and earlier prediction of preeclampsia may offer a better opportunity for prophylactic intervention with medications such as aspirin or nitric oxide donors.

The strengths of this study were that we applied a strict definition of preeclampsia and that patients satisfied this definition after chart review. We did not rely on patient recall or discharge codes for the diagnosis of preeclampsia. We also excluded patients from the study if they had a condition or were using a medication that could affect cerebral hemodynamics.

Based on these data, we believe that TCD indices of low MCA resistance in the second trimester are predictive of impending preeclampsia. These results justify a larger trial to confirm the findings in a more ethnically diverse population and at an earlier gestational age. MCA resistance indices may provide an important prenatal screening test for preeclampsia.

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# CHAPTER 9

## SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

## 9.1 Introduction

Advances in measurement techniques and methods have made it possible to study dynamic changes in blood pressure (BP) and cerebral blood flow (CBF), and consequently cerebral autoregulation (CA). In this thesis, these techniques have been applied to normal and complicated pregnancies.

This chapter will provide a summary of the findings in this thesis, followed by a general discussion of (i) the cerebral hemodynamics in normal and complicated pregnancy, (ii) the possibility of predicting preeclampsia, and (iii) perspectives for further research.

## 9.2 Summary

Previous studies have demonstrated significant changes in cerebral hemodynamics normal pregnancy. Most of these data are derived from the middle cerebral artery, showing decreases in the velocity and resistance index.[1, 2] However, the posterior circulation is believed to be more vulnerable to dysfunctional cerebral autoregulation because of its relative lack of sympathetic innervation,[3] and as an extension of this, eclampsia is sometimes hypothesized to be an expression of the posterior reversible encephalopathy syndrome.[4]

In **chapter 2,** the effect of gestational age on cerebral blood flow in the anterior and posterior cerebral arteries during normal pregnancy was investigated. A decrease in the anterior cerebral artery (ACA) systolic and mean velocity was found, similar to velocity changes in the middle cerebral artery (MCA),[1] while the diastolic velocity in the posterior cerebral artery (PCA) increased. The common hypothesis is that MCA changes are due to increased vascular distensibility. In both ACA and MCA, RI showed a peak during the second trimester of pregnancy, decreased during the third trimester, then subsequently increased in the postpartum period. The magnitude of the third trimester decrease in RI was smaller for the PCA than for the ACA, which is consistent with the increased diastolic and systolic velocities in the PCA. These results, combined with previously published longitudinal MCA data,[1] show a reduction in velocity in the anterior circulation (MCA and ACA), and an increase in velocity in the posterior circulation (PCA) during normal pregnancy. This might indicate a redistribution of cerebral blood flow from the

anterior territory to the posterior, and may explain the characteristic predominantly posterior brain involvement in women who develop eclampsia.[5, 6]

These cerebrovascular hemodynamic changes, combined with the systemic cardiovascular changes of pregnancy are remarkable, since the cerebral circulation is dependent on a constant blood supply and is relatively intolerant to increases or decreases in blood volume. The physiological process by which the cerebral blood flow is maintained at an optimal level despite changes in blood pressure is called cerebral autoregulation. **Chapter 3** describes increased cerebral autoregulation functionality in the second half of pregnancy, as indicated by the autoregulation index (ARI), when compared to non-pregnant women of reproductive age. Unlike the velocity changes seen in the cerebral arteries, the cerebral autoregulation did not change with gestational age. The autoregulation index is significantly higher in pregnancy, even after controlling for end-tidal $CO_2$, but the timing of when this occurs remains unclear since only women after 20 weeks of gestation were included.

In **chapter 4,** the autoregulation index of normotensive pregnant women was compared with patients with preeclampsia who were studied prior to receiving treatment. The cerebrovascular complications seen in preeclampsia have been hypothesized to be due to impaired cerebral autoregulation. This may explain the development of eclampsia or other cerebral complications that may occur without sudden or excessive elevation in blood pressure. We demonstrated that the autoregulation index was indeed significantly reduced in preeclamptic women. Although there was no correlation between the ARI and blood pressure, the three patients with the lowest autoregulation index scores (ARI <3) all had chronic hypertension with superimposed preeclampsia requiring two or more antihypertensive agents to control their BP. In addition to changes in the autoregulation index, we also found statistically significant differences in resistance index, pulsatility index, resistance-area product, and cerebral perfusion pressure. Women with superimposed preeclampsia were shown to have a reduced autoregulation index when compared to those with new onset preeclampsia. **(chapter 6)**, but the autoregulation index in new onset preeclampsia was still lower than that seen in

the control group. Gestational hypertension (GHTN), which is also characterized by new-onset hypertension (but without proteinuria) was not associated with changes in the autoregulation index.

In **chapter 5,** cerebrovascular hemodynamics in preeclamptic women and normotensive controls were further studied by evaluating the cerebrovascular response to breath holding. Deep breath holding is associated with complex chemical ($PaCO_2$), mechanical (changes in blood pressure and heart rate), and neural (autonomic nervous system) consequences, all of which affect cerebral blood flow. Cerebral blood flow velocity (CBFV) changes were broken down into standardized subcomponents describing the relative contributions of blood pressure, cerebrovascular resistance index (CVRi), critical closing pressure (CrCP), and resistance area product (RAP). The area under the curve (AUC) was then calculated for changes in relation to baseline values. While the increase in CBF velocity and end-tidal $CO_2$ was similar in both groups, the AUC for CVRi and RAP during breath holding was significantly different between the groups, indicating an early, transient increase in CVRi and RAP in the control group, which was absent in preeclampsia. Blood pressure had an equal contribution in both groups. We hypothesize that this difference is due to a blunted sympathetic or impaired myogenic cerebral vasoconstriction response in women with preeclampsia. The reduced vasoconstrictor response may be similar to what has been described in acute stroke patients.[7] Because the subcomponent peak of CrCP was equal in the groups, our study suggests that the metabolic pathway is intact, at least during the relatively small demand of a short breath hold.

Some chronic conditions, including hypertension, diabetes and obesity, are known to increase the risk of developing preeclampsia. The cerebral autoregulation of these were studied in Chapter 6 and 7.

In **chapter 7** the impact of diabetes and obesity on cerebral autoregulation in pregnancy was assessed. Diabetes and obesity are not only risk factors for the development of preeclampsia, but also for cardiovascular complications, both of which are associated with endothelial dysfunction. Based on the increased risks for developing preeclampsia and cerebrovascular complications in patients with pregestational diabetes type 2 (DM2), but a less pronounced relationship with gestational diabetes (GDM), we hypothesized that the cerebral

autoregulation is impaired in DM2, but not in GDM. However, the autoregulation index in pregnant women with either diabetes or overweight, was not significantly different to that in healthy pregnant controls. Furthermore, there were no differences in the autoregulation index between women with diet or medication controlled gestational diabetes or DM2. It has to be noted that none of the study participants were known to have microvascular complications or autonomic neuropathy, which are thought to be associated with cerebral autoregulation impairment in DM. Also, all participants had excellent glycemic control (as shown by daily glucose monitoring). Therefore, relatively mild hyperglycemia and short disease duration likely allow for preserved cerebral autoregulation. These findings suggest that if such women are at an increased risk for preeclampsia based on their diabetic and/or high BMI status, it is unlikely to be associated with significant impairment in dynamic cerebral autoregulation prior to the development of the hypertensive state.

Women with chronic hypertension have an increased risk of developing super-imposed preeclampsia, and the risk for cerebrovascular complications during pregnancy is increased with all hypertensive disorders, but is most pronounced with severe preeclampsia and super-imposed preeclampsia. As with diabetes and obesity, these complications are believed to be caused by impaired cerebral autoregulation. In **chapter 6** it was shown that the autoregulation index is significantly reduced in CHTN. There was no difference in autoregulation index between women with CHTN who were using antihypertensive medication versus those who were not.

In chapter 6 and 8, we investigated whether analysis of the different components of cerebral hemodynamics can identify those pregnant women who are destined to develop preeclampsia. While the development or progression of the disorder cannot be prevented, identification of women at risk will aid in early diagnosis and appropriate management, and may improve maternal and perinatal outcome.[8]

In **chapter 6,** a prospective cohort study was performed to study the autoregulation index in normotensive and hypertensive pregnancy. Seven patients (23%) with CHTN, 3 patients (10%) in the control group, and 5 patients (25%) with GHTN were studied who

subsequently developed preeclampsia, and were compared to patients who did not develop preeclampsia. The autoregulation index of women with CHTN who subsequently experienced preeclampsia was lower compared with those who did not. This was not true for women with GHTN or control subjects who later experienced preeclampsia.

In **chapter 8,** the cerebral hemodynamics of the MCA in 405 low-risk women in the second trimester of pregnancy were studied. MCA velocity, resistance index (RI), pulsatility index (PI) and cerebral perfusion pressure (CPP) were evaluated as potential predictors for the future development of preeclampsia. Seven (1.7%) subjects subsequently did develop preeclampsia. RI and PI values were lower in these seven women. Other measurements and derived values describing cerebrovascular flow and resistance were not significantly different at the time of measurement, but mean systemic blood pressure was higher. An RI of < 0.54 and a PI of < 0.81 were clinically useful in predicting subsequent preeclampsia. Areas under the receiver–operating characteristic curves for RI and PI were 0.93 and 0.93, respectively, with optimal sensitivity and specificity of 86% and 93% for both variables. Positive and negative likelihood ratios were 11.8/0.15 (RI) and 12.3/0.15 (PI). These data suggest that transcranial Doppler indices of low MCA resistance in the second trimester are predictive of the subsequent development of preeclampsia.

## 9.3 General discussion

*9.3.1 Cerebral hemodynamics in pregnancy*

While the systemic circulation undergoes extensive changes during pregnancy, the brain is dependent on a constant blood supply, and relative intolerance to increases or decreases in blood volume. Previous studies have shown a decrease in blood flow velocity (transcranial Doppler) or blood flow (MRI) in the middle cerebral artery (MCA).[1, 9, 10]

The MCA is the largest of the cerebral arteries and supplies most of the cerebral hemisphere and deep subcortical structures, but the posterior cerebral artery (PCA) is believed to be more vulnerable to dysfunctional cerebral autoregulation in preeclampsia.[3] In **chapter 2,** a decrease in the anterior cerebral artery (ACA) systolic and mean

velocity during normal pregnancy was described, similar to the velocity changes in the MCA.[1] The diastolic velocity in the PCA, however, increased.[11] This suggests that during normal pregnancy, there may be some degree of redistribution of cerebral blood flow from the MCA and ACA territory to that of the PCA. This redistribution may explain the vulnerability of the posterior circulation.[5, 6] Several studies, predominantly performed in animals, have shown attenuated sympathetic innervation of the posterior cerebral circulation (vertebrobasilar arteries) when compared with the anterior circulation (MCA and ACA, arising from internal carotid arteries),[3] and less effective autoregulation during pregnancy.[12]

In **chapter 3,** enhanced cerebral autoregulation functionality was shown in the second half of pregnancy, when compared to non-pregnant fertile women. This improved autoregulation was independent of gestational age, and remained significant even after controlling for end-tidal $CO_2$ ($EtCO_2$).[13] This is in accordance with previous studies in both human[14] and rats.[15, 16]

The alterations seen in cerebral hemodynamics during pregnancy might be caused by a combination of changes in carbon dioxide, hormones, cytokines, and other circulating factors,[12] as well as changes in perivascular innervation.[17] The individual differences between the anterior and posterior circulations, as regards to their specific adaptations to pregnancy may reflect a variable sensitivity of these vessels to these changes.

The pregnant state is characterized by respiratory alkalosis and hypocapnia. A decrease in $PaCO_2$ is known to cause physiologic vasoconstriction, increased cerebrovascular resistance and decreased cerebral blood flow velocity due to constriction of the small arteries.[18, 19] This also leads to an improved autoregulatory capacity.[20]

However, as said, the autoregulatory functionality (ARI) was significantly higher in pregnancy, even after controlling for $EtCO_2$. Furthermore, the resistance index (RI), often interpreted as an indicator of cerebrovascular resistance, decreased in the second half of pregnancy in both ACA and PCA, while the blood flow velocity increased in the PCA and decreased in the ACA. These results may indicate that $PaCO_2$ is not a main determinant of cerebrovascular changes in pregnancy, and/or that the relationship between RI and

cerebrovascular impedance is more complex. The lower cerebrovascular resistance in pregnant rats has been explained by outward remodeling of parenchymal arterioles and increased capillary density coupled with the physiologic hemodilution seen in pregnancy.[17]

During pregnancy, estrogen levels rise until term. Estrogens have a vasodilatory effect on the microvasculature[21] through endothelial nitric oxide (NO) synthase.[22] Indeed, cerebral blood flow declines with he onset of menopause and increases with hormone replacement therapy.[23, 24] By studying the effect of ovarian suppression and stimulation, a significant correlation between increased estrogen levels and increased blood flow velocity in the internal carotid artery has been shown together with a concomitant decrease in cerebrovascular resistance.[25] In **chapter 3** it was demonstrated that RI decreased during pregnancy in both the ACA and the PCA and increased postpartum. Cipolla *et al*. have shown gestation-induced changes in endothelial and neuronal nitric oxide synthase[17] in Sprague-Dawley rats and significantly decreased nitric oxide synthase expression in their anterior versus posterior cerebral cortex.[12] Such regional differences might explain the different slopes seen in the study described in **chapter 3**. However, studies evaluating the role of NO on the human cerebral autoregulation are sparse, and have shown conflicting results, reporting impaired autoregulation following NO inhibition,[26] and no effect[27]

Other factors that might be involved in the enhancement of autoregulatory capacity could be the renin-angiotensin system (RAAS),[28] the perivascular innervation, vascular structure or cytokines, all known to be altered in preeclampsia.[17]

Better understanding of the factors affecting cerebral hemodynamics in normal pregnancy might help shed light on the pathophysiology of complications seen in hypertensive pregnancies. The timing of changes during pregnancy and postpartum and the mechanism by which pregnancy enhances cerebral autoregulation functionality have yet to be explored.

*9.3.2 Cerebral autoregulation in hypertensive pregnancy*

The cerebrovascular complications seen in preeclampsia have been hypothesized to be caused by impaired cerebral autoregulation.

This may explain the seemingly insidious development of eclampsia or other cerebral complications without sudden, or excessive elevation in blood pressure.

**Chapter 4 and 6** showed that cerebral autoregulation is indeed impaired in pregnant women with preeclampsia and even more in superimposed preeclampsia.[29, 30] Interestingly, there was no correlation between the autoregulatory index (ARI) and blood pressure, and impaired autoregulation could not be identified based on clinical symptoms such as headache or visual disturbances. However, the largest degree of impairment was found in women with superimposed preeclampsia who required two or more antihypertensive drugs to control their blood pressure.[30] Furthermore, the functionality of autoregulation (ARI) is impaired in pregnant women with chronic hypertension, and especially in those with chronic hypertension who subsequently experienced superimposed preeclampsia when compared with women who did not progress to preeclampsia.[29] The ARI of patients with new onset preeclampsia was not much different from the ARI of patients with chronic hypertension[29] and the ARI of women with gestational hypertension was similar to those with normotensive pregnancy.

The spectrum of conditions (which ranged from superimposed preeclampsia, preeclampsia, and chronic hypertension to gestational hypertension and control subjects), along with their associated spectrum in ARI, might reflect a range of endothelial impairment. Although preeclampsia is defined by hypertension and proteinuria, it involves multiple organ systems (e.g. renal, liver, brain, vascular, coagulation, placenta) that may lead to different pathophysiological phenotypes. These phenotypes, combined with the heterogeneity in disease severity may explain the large range seen in ARI in preeclampsia.

Previous studies suggest that altered expression of angiogenic factors produces systemic endothelial dysfunction and plays an important role in the pathogenesis of preeclampsia.[31] The extent of these deviations depends on the type of hypertensive disorder, being more pronounced in preeclampsia than in women with chronic and gestational hypertension when compared with control subjects.[32-34] Another study found an altered angiogenic balance in preeclampsia,

but not in gestational hypertension.[35] The proteinuria that is seen in preeclampsia is caused by renal endothelial dysfunction and is also suggested to be related to this angiogenic inbalance.[31] These results are in agreement with the findings in **chapter 6** – i.e. lowest ARI in the preeclampsia group and similar ARI in women with gestational hypertension and control group.

In addition to ARI, resistance area product (RAP) and critical closing pressure (CrCP) were also studied in **chapter 6**. Women with gestational hypertension and preeclampsia were found to have a higher RAP - which is thought to reflect myogenic activity[36] - but decreased CrCP - indicative of metabolic control[36]-, which counteracts the effect of RAP and suggests an abnormal neurovascular coupling. These changes were not seen in patients with chronic hypertension. Previous studies using transcranial Doppler have also shown an impaired response to $CO_2$ inhalation in patients with preeclampsia[37], but not with chronic hypertension.[38]

A difference in cerebrovascular response to a breath holding challenge between normotensive controls and patients with preeclampsia was also seen **(chapter 5)**.[39] In addition to influencing $PaCO_2$, deep breath holding also affects the sympathetic nervous system via the diving reflex,[40] resulting in changes in cerebral blood flow velocity (CBFV), blood pressure and cerebrovascular resistance (represented by either the cerebrovascular resistance index (CVRi) or combined CrCP and RAP). Although the CBFV and blood pressure responses were similar in both groups, patients with preeclampsia lacked a transient increase in both CVRi and RAP during the initial phase of the breath holding maneuver.[39] We hypothesized that this was due to a blunted sympathetic or impaired myogenic cerebral vasoconstriction response in women with preeclampsia. The similar subcomponent peak of CrCP between the groups suggests that the metabolic pathway during the relatively small demand of a short breath hold is intact.

While it now seems evident that cerebral hemodynamics are affected by preeclampsia, the timing of these changes and the impact of neurological, laboratory or degree of endothelial dysfunction are not known. Much more future research is needed to elucidate these factors.

*9.3.3 Cerebral autoregulation in pregnancies complicated by diabetes, obesity and chronic hypertension*

Women with chronic hypertension, pre-pregnancy diabetes mellitus (DM2), and obesity have a substantially increased risk of preeclampsia compared with women without such risk factors. The association between preeclampsia and gestational diabetes is less pronounced.[41, 42] This inconsistency is likely to be due to heterogeneity of the population with gestational diabetes, with regard to the degree of impaired glucose metabolism, glycemic control, and its time of onset during pregnancy. Further confounding the association is that women with gestational diabetes often have co-existing obesity, which in itself is an independent risk factor for preeclampsia.[43, 44]

The mechanisms by which these conditions increase preeclampsia risk are largely unknown, but these risk factors are associated with underlying maternal endothelial dysfunction. The latter might also affect the cerebral autoregulation and may increase susceptibility of the vasculature to the hemodynamic changes in pregnancy.[31] Indeed, these women develop preeclampsia in smaller increments of angiogenic factor dysregulation.[31, 34] This angiogenic dysregulation is thought to produce systemic endothelial dysfunction and to be responsible for the clinical manifestations of preeclampsia.[31]

**Chapter 7** showed that cerebral autoregulation is not impaired in women with (uncomplicated and non-vasculopathic) diabetes in pregnancy. Furthermore, the functionality of autoregulation (ARI) is equally effective in euglycemic women with and without prepregnancy obesity.[45]

Other studies on cerebral autoregulation in non-pregnant patients with type 2 diabetes mellitus have shown conflicting results, with both normal autoregulation[46, 47] and affected dynamic autoregulation with[48] and without[48, 49] the presence of microvascular disease. However, comparison with these studies is difficult due to differences in age, disease duration and severity, and gender. None of the patients studied in **chapter 7** had microvascular complications or autonomic neuropathy, both of which are thought to be associated with impairment of cerebral autoregulation in diabetes.[47, 50] In pregnancy, these factors (characterized by baseline proteinuria and the stage of the disease according to the White classification) are associated with

the development of preeclampsia.[51] None of the women studied in **chapter 7** had baseline proteinuria or class D diabetes or higher which might explain the lack of impaired autoregulation. Furthermore, interpretation of previous studies on gestational diabetes and adverse pregnancy outcomes has been complicated by the fact that these studies were not differentiated according to disease severity.[41, 42] In **chapter 7** both diet- and medication controlled gestational diabetes were studied separately, but there was no difference in autoregulation in either of these sub groups. As in the patients with type 2 diabetes in **chapter 7**, we hypothesized that the excellent glycemic control (as shown by daily glucose monitoring), relatively mild hyperglycemia and short disease duration allow for preserved cerebral autoregulation. Another explanation for the absence of impaired autoregulation might be pregnancy in and of itself, since pregnancy, as described above, has been shown to enhance autoregulation.[13] Lastly, in **chapter 7** autoregulation was only studied within the context of spontaneous fluctuations in blood pressure during rest, which is mainly a myogenic activity. Therefore, the possibility of cerebral blood flow changes induced by metabolic activity such as might be present in patients with impaired $PaCO_2$ cerebrovascular reactivity can not be excluded.[46]

The findings in **chapter 7** suggest that the increased risk for preeclampsia in patients with (pre-)gestational diabetes and/or overweight is unlikely to be associated with significant impairment in dynamic cerebral autoregulation prior to the development of the hypertensive state. Whether this holds true for patients with advanced diabetic complications remains to be determined.

In contrast to what is seen in diabetes and overweight status, chronic hypertension, which is also associated with maternal endothelial dysfunction, does in fact affect cerebral autoregulation in pregnancy **(chapter 6)**. Women with chronic hypertension had a significantly decreased autoregulation index (ARI) when compared to normotensive controls. This was even true after excluding those women who subsequently developed superimposed preeclampsia. These results may explain the reason why women with chronic hypertension or preeclampsia have an increased risk for developing cerebral complications such as stroke during pregnancy, even without sudden or excessive elevation in blood pressure.[52, 53]

The cerebral autoregulation in pregnancies complicated by chronic hypertension is discussed in more detail in the following section.

*9.3.4 Prediction of preeclampsia*

Although there is no proven effective method for the prevention of preeclampsia, identifying women at risk would allow individually tailored antenatal care and early delivery if needed, thereby reducing the risk of developing severe complications.

Previous studies have used different risk factors including clinical history, complete blood count and biochemical markers to predict preeclampsia, with conflicting results.[8, 33, 54] The cerebral hemodynamics have been studied in normotensive and hypertensive pregnancy by using transcranial Doppler ultrasound and velocity-encoded phase-contrast magnetic resonance imaging (MRI).[55, 56]

**Chapter 8** suggests that transcranial Doppler indices of low resistance in the middle cerebral artery in the second trimester are predictive of the subsequent development of preeclampsia in a low-risk, ethnically homogeneous population.[57] This supports previous studies showing a reduced resistance index and/or pulsatility index either before[58] or after[59-61] the clinical development of preeclampsia. The results are also consistent with studies that show preeclampsia to be characterized by a hyperdynamic state with elevated cardiac output and reduced peripheral resistance early in pregnancy.[62, 63] The patients studied in **chapter 8** who developed preeclampsia all had a relatively mild and late-onset disease. This supports the suggestion of Valensise *et al*.[64] that women likely to develop early-onset pre-eclampsia (< 34 weeks) show elevated peripheral vascular resistance before the onset of hypertension and proteinuria, while those who will develop preeclampsia late in pregnancy have an initially low vascular resistance.[64] The results in **chapter 8** are consistent with this proposal: six of seven preeclamptic patients were diagnosed at or after 34 weeks' gestation.

**Chapter 6** evaluates the cerebral autoregulation in hypertensive disorders of pregnancy (superimposed preeclampsia, preeclampsia, chronic hypertension and gestational hypertension vs. controls), including a subgroup analysis of women who did or did not develop preeclampsia. Resistance and pulsatility indices were indeed decreased

in women with chronic hypertension who subsequently developed superimposed preeclampsia (data not shown). This was not the case for women with chronic hypertension who did not progress to superimposed preeclampsia or the control group. Only three women in the control group (10%) developed preeclampsia, and one of them developed early onset preeclampsia (gestational age 31+6 weeks). She did in fact demonstrate increased pulsatility and resistance indices.

Riskin-Mashiah *et al*.[58] also showed that decreased cerebral resistance indices predicted the subsequent development of preeclampsia. However, two cerebral autoregulatory challenge tests at the time of examination ($CO_2$ inhalation and hand grip), showed a normal vasodilatory response, suggesting intact autoregulation.[58] **Chapter 6** demonstrates that the autoregulation index of normotensive women was not predictive of the development of preeclampsia.[29] Janzarik *et al*.[14] also did not find impairment of cerebral autoregulation as an early feature of preeclampsia.

In light of the angiogenic dysregulation prior to the clinical presentation of preeclampsia it is now suggested that the cerebrovascular resistance changes prior to the development of preeclampsia does not represent cerebrovascular dysfunction, but rather a physiologic compensatory response.

As was true for normotensive women, women with gestational hypertension who did or did not progress to preeclampsia had similar autoregulation indices (ARIs). However, women with chronic hypertension who subsequently experienced preeclampsia had lower ARIs compared with those who did not. Their ARI was comparable to patients who already had superimposed preeclampsia. There are two possible explanations for this finding. First, the changes in cerebral autoregulation may occur prior to the manifestations of clinical symptoms of superimposed preeclampsia, reflecting early manifestation of disease or the underlying pathophysiology. This is further supported by the finding that chronic hypertension outside of pregnancy does not appear to alter cerebral autoregulation, even in sustained untreated middle-aged and older people.[65-67] In addition, lower MCA resistance in low risk pregnant women in the second trimester, who likely lacked endothelial dysfunction at the time of examination, predicted the development of PE.[57] These findings, together with evidence that angio-

genic factors have been detected in maternal serum 5 to 10 weeks prior to the onset of preeclampsia, suggest that ARI may indeed be impaired in these cases well before the clinical manifestation of disease.[31, 32, 35] If this is in fact true, ARI can potentially be used as a screening tool.

A second explanation may be that reduced ARI is indicative of baseline endothelial dysfunction, making pregnant women with chronic hypertension more susceptible for developing superimposed preeclampsia. This is supported by the finding that women with chronic hypertension or diabetes develop preeclampsia at a lower level of angiogenic disturbance,[33] and would also explain why the ARI in women with gestational hypertension and controls was normal. To take this a step further, in chronic hypertension, endothelial function is already impaired while the angiogenic imbalance may cause a second hit and the clinical manifestation of superimposed preeclampsia. This theory is in agreement with Noori *et al*., who found impaired endothelial function in the brachial artery prior to the alteration of angiogenic factors.[35]

Even though this theory is attractive, the study in **chapter 6** was not designed to determine whether autoregulation index can be used as a predictor for preeclampsia, and results should therefore be interpreted with caution. Whether the lower ARI is due to preexistent differences or early affected cerebral circulation in pregnant women with chronic hypertension remains to be determined.

The two studies in low risk women in **chapters 6 and 8** show a striking difference in the incidence of preeclampsia. In chapter 8, only 7 out of the 405 women studied (1.7%) developed preeclampsia.[57] In the other study, 10% developed preeclampsia (3/30).[29] The specific characteristics of the populations studied might explain this difference. The first one was conducted in a low-risk, middle- class, almost exclusively Caucasian population (92%), with a very low regional incidence of preeclampsia. In the second study only 43% of the control group was of Caucasian ethnicity and participating women had a higher pre-pregnancy BMI. Information on the socioeconomic status of the women in this study is unfortunately not available. Both ethnicity and pre-pregnancy BMI are known to be independently associated with the development of preeclampsia and can, at least partly, explain this difference in incidence of preeclampsia.

*9.3.4 Final conclusions*

1. Normal pregnancy causes a redistribution of the cerebral blood flow from the anterior to the posterior circulation. This redistribution may explain why the posterior circulation is most vulnerable to cerebrovascular complications in preeclampsia and eclampsia.

2. Cerebral autoregulation functionality of the middle cerebral artery is enhanced in the second half of normal pregnancy, and is independent of gestational age. This remains true even after controlling for end-tidal CO2, which is physiologically lower in pregnancy.

3. Cerebral autoregulation functionality (ARI) is impaired in preeclampsia and even more so in superimposed preeclampsia. There is no correlation between the autoregulatory index and blood pressure. This may explain the development of eclampsia or other cerebral complications without sudden, or excessive elevation in blood pressure.

4. Women with preeclampsia show a difference in cerebrovascular response in the initial phase of a breath holding maneuver. This might be due to a blunted sympathetic or impaired myogenic cerebral vasoconstriction response in preeclampsia, while the metabolic pathway during this relatively small demand of a short breath hold appears to be intact.

5. Cerebral autoregulation is impaired in women with chronic hypertension, and especially in those with chronic hypertension who subsequently experienced superimposed preeclampsia when compared with women who did not progress to superimposed preeclampsia.

6. Cerebral autoregulation is not impaired in gestational hypertension, well-controlled (pre-)gestational diabetes or in overweight women.

7. Indices of low middle cerebral artery resistance as derived by transcranial Doppler in the second trimester are predictive of the subsequent development of preeclampsia in a low- risk, ethnically homogeneous population.

8. The cerebral autoregulation in women with normal blood pressure and with gestational hypertension is similar for those who do and do not progress to preeclampsia. However, this functionality of women with chronic hypertension who subsequently experience superimposed preeclampsia is lower compared with those who do not.

*9.3.5 Future perspectives*

1. The details of how pregnancy affects cerebral blood flow and cerebral autoregulation is largely unknown. Better understanding of the factors affecting cerebral hemodynamics in normal pregnancy might help understand the pathophysiology of complications seen in hypertensive pregnancies. The timing of changes during pregnancy and postpartum and the mechanisms by which pregnancy enhances cerebral autoregulation functionality have yet to be explored. This should preferably by studied using longitudinal studies with measurements before, during, and after pregnancy.

2. In this thesis, the middle cerebral artery was predominantly studied, but the posterior cerebral artery is believed to be more vulnerable to dysfunctional cerebral autoregulation in preeclampsia. Future research should focus on the posterior circulation in normal pregnancy and preeclampsia.

3. It seems evident that cerebral hemodynamics are affected by preeclampsia, and some of the possible cofounders were studied in the different chapters. However, increasing the statistical power of studies, might provide a more consistent picture of what is happening when considering all co-factors included.

4. The timing of the changes in the cerebral hemodynamics seen in patients with preeclampsia and the impact of neurological, laboratory or the degree of endothelial dysfunction are not known. Future research is needed to elucidate these factors. Patients with severe preeclampsia are treated with magnesium sulfate for seizure prophylaxis while the specific mechanisms of action remain unclear. Previous studies using transcranial Doppler have shown changes in cerebral hemodynamics after administration of magnesium sulfate and future studies should elaborate on this.

5. Cerebral autoregulation assessed in the middle cerebral artery was shown to be impaired in women with chronic hypertension who subsequently experienced superimposed preeclampsia well before the clinical manifestation of disease. A prospective longitudinal study including pregnant women with chronic hypertension should be performed to further elucidate this and evaluate the possibility of using autoregulation as a screening tool.

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# HOOFDSTUK 10

## NEDERLANDSE SAMENVATTING

Tijdens de zwangerschap ontwikkelt 6-25% van de vrouwen een hoge bloeddruk. Het is een van de meest voorkomende oorzaken van het overlijden of ontwikkelen van een ernstige handicap van de moeder. Deze hoge bloeddruk (hypertensie) kan in verschillende vormen bestaan: Chronische hypertensie (hypertensie al voor de zwangerschap aanwezig), zwangerschapshypertensie (hypertensie ontstaan in de zwangerschap), preeclampsie (hypertensie en eiwit in de urine, in de volksmond bekend als zwangerschapsvergiftiging) gesuperponeerde preeclampsie (preeclampsie bij een zwangere met chronische hypertensie), en eclampsie (epileptische aanval bij pre-eclampsie).

Door de hoge bloeddruk kunnen verschillende organen aangetast worden, maar het meest gevreesd is hersenschade. Het risico hierop is vergroot bij alle vormen van hypertensie, maar het meest bij ernstige preeclampsie. De klachten (cerebrovasculaire complicaties) variëren van hoofdpijn en stoornissen in het gezichtsvermogen, epilepsie en veranderingen in bewustzijn tot hersenbloedingen. Hierbij is met name de achterzijde van de hersenen (parieto-occipitaal kwab) aangedaan. De exacte manier waarop preeclampsie deze klachten veroorzaakt is niet bekend, maar gedacht wordt dat de bloedvaten in de hersenen minder goed werken. Normaal is de doorbloeding van de hersenen (cerebrale circulatie) constant, ondanks veranderingen in de bloeddruk. Dit wordt de cerebrale autoregulatie genoemd. Dit mechanisme beschermt tegen het ontstaan van een hersenbloeding wanneer de bloeddruk stijgt, en beschermt tegen flauwvallen wanneer de bloeddruk daalt. Vrouwen met preeclampsie kunnen te maken krijgen met cerebrovasculaire complicaties terwijl hun bloeddruk niet heel hoog is.

De cerebrale autoregulatie kan worden bepaald door tegelijk de bloeddruk met een drukmeter op de vinger (arterial volume clamping) en de doorbloeding van het middelste bloedvat in de hersenen (de arteria cerebri media, met transcraniële Doppler) te meten. Dit wordt de autoregulatie index (ARI) genoemd. Deze methode wordt al veel gebruikt in onderzoek naar beroertes en hersenschade na ongelukken.

Hiernaast kan met de transcraniële Doppler ook de weerstand in de hersenvaten en de bloedstroomsnelheid op zich bekeken worden. Eerdere onderzoeken naar de cerebrale circulatie in preeclampsie

hebben laten zien dat de bloeddoorstroming of het bloedvolume in hersenen van vrouwen met preeclampsie verhoogd is. Daarnaast reageren de hersenvaten minder goed op verhoging van het $CO_2$ in het bloed (wat er normaal voor zorgt dat de vaten wijder worden).

Het doel van het onderzoek in dit proefschrift was om de cerebrale autoregulatie van zwangere vrouwen die te maken krijgen met hoge bloedddruk te vergelijken met zwangere vrouwen die een normale bloeddruk hebben. Zoals gezegd wordt gedacht dat de cerebrale autoregulatie minder werkt bij vrouwen met preeclampsie, maar dat is nog niet in mensgebonden onderzoek aangetoond. Om te kunnen zien wat afwijkend is, moet eerst worden vastgesteld wat normaal is. Daarom werd ook onderzocht hoe de hersendoorbloeding en de autoregulatie gedurende de normale zwangerschap verandert, en of het op basis hiervan te voorspellen is of een zwangere preeclampsie zal ontwikkelen later in de zwangerschap.

Hoofdstuk 1 is een inleiding van het proefschrift. Hierin werden de verschillende vormen van hypertensie in de zwangerschap nader beschreven en werd de pathofysiologie van preeclampsie uitgelicht. Ook werd de methodiek van het bepalen van de autoregulatie index (ARI) en andere parameters van de cerebrale circulatie uitgelegd.

In hoofdstuk 2 werd het effect van het vorderen van de zwangerschapsduur op twee hersenvaten (arteria cerebri anterior (ACA) en arteria cerebri posterior (ACP)) onderzocht, de arteria cerebri media (ACM) was in dit kader al eerder onderzocht. Het onderzoek toonde aan dat de bloedstroomsnelheid in de voorste circulatie (ACA+ACM) afnam en in de achterste circulatie (ACP) juist toenam tijdens de normale zwangerschap. Dit kan wijzen op een redistributie van de hersendoorbloeding naar de achterste circulatie, en zou een verklaring kunnen zijn waarom dit gebied het meest kwetsbaar is bij preeclampsie en eclampsie.

Hoofdstuk 3 beschrijft de cerebrale autoregulatie in de tweede helft van de zwangerschap. De ARI bleek constant in deze periode, maar was vergeleken met niet zwangeren in de zelfde leeftijd wel

significant hoger. Dit verschil bleef aanwezig wanneer er voor het lagere $CO_2$ gehalte gecompenseerd werd (Een lager $CO_2$ geeft een beter werkende cerebrale autoregulatie en zwangere vrouwen hebben altijd een lager $CO_2$).

De reden van deze veranderingen in de cerebrovasculaire circulatie is niet duidelijk, maar is waarschijnlijk een combinatie van veranderingen in $CO_2$, hormonen, cytokines en de zenuwen die zich rondom de bloedvaten bevinden. Het gevonden verschil tussen de voorste en achterste circulatie kan dan veroorzaakt zijn door een meer of mindere gevoeligheid voor deze veranderingen.

Verder onderzoek zal meer inzicht moeten geven in deze veranderingen en het moment van veranderingen in de zwangerschap en na de bevalling. Deze informatie van het normale verloop kan helpen het abnormale, zoals bij hypertensie in de zwangerschap, beter te begrijpen.

In hoofdstuk 4 werd de cerebrale autoregulatie van zwangere vrouwen met preeclampsie vergeleken met gezonde zwangere vrouwen. De hypothese dat deze autoregulatie is aangedaan bij preeclampsie bleek te kloppen. Er was echter geen verband tussen de ARI en de bloeddruk zelf. Wel bleek dat de 3 patiënten met de laagste ARI allen chronische hypertensie, en dus gesuperponeerde preeclampsie hadden, waarvoor zij 2 of meer medicijnen nodig hadden om de bloeddruk te verlagen.

Naast de autoregulatie werden door middel van ademinhouden andere functies van de cerebrovasculaire circulatie in preeclampsie onderzocht. Het vasthouden van de adem zorgt, naast stijging van het arteriële $CO_2$, ook voor veranderingen in bloeddruk, hartfrequentie en het autonome zenuwstelsel, welke op hun beurt weer de cerebrale circulatie beïnvloeden.

In hoofdstuk 5 werden veranderingen in de cerebrale bloedstroomsnelheid uitgedrukt in veranderingen in bloeddruk, cerebrovasculaire weerstand (CVRi), critical closing pressure (CrCP) en resistance area product (RAP). Vervolgens werd de area under the curve (AUC) vergeleken met de normaalwaarden voor het adem inhouden.

Hoewel de toename in stroomsnelheid en $CO_2$ vergelijkbaar was in gezonde zwangere en zwangeren met preeclampsie, bleek de AUC voor de CVRi en RAP verschillend: een vroege, tijdelijke toename in CVRi en RAP was wel aanwezig bij de gezonde zwangeren, maar niet bij preeclampsie. Dit verschil wordt mogelijk veroorzaakt door een afgenomen sympathische of myogene cerebrale vasoconstrictie bij preeclampsie. Eenzelfde verschil is eerder gezien bij mensen met een beroerte. De metabole response tijdens deze relatief kleine stressepisode leek wel intact te blijven.

De autoregulatie in verschillende vormen van hoge bloeddruk in de zwangerschap werd verder onderzocht in hoofdstuk 6. De verminderde werking van de cerebrale autoregulatie in vrouwen met gesuperponeerde preeclampsie vergeleken met nieuw ontstane hoge bloeddruk en preeclampsie werd bevestigd. Maar ook de laatste groep had een significant lagere ARI vergeleken met de controle groep van zwangere vrouwen met een normale bloeddruk. Verder bleek dat vrouwen met zwangerschapshypertensie (dus zonder eiwit in de urine (proteïnurie)) een normale autoregulatie voor de zwangerschap hadden. Dit verschil tussen vrouwen met en zonder proteïnurie zou verklaard kunnen worden door het in meer of mindere mate aanwezig zijn van endotheeldysfunctie. Endotheel (een bedekkende laag cellen aan de binnenkant van onder andere bloedvaten) speelt een belangrijke rol bij de ontwikkeling van preeclampsie en is belangrijk voor een goed werkende autoregulatie. Endotheeldysfunctie is bijvoorbeeld ook aan de orde bij een beroerte of hartaanval.

In hoofdstuk 6 en 7 werden zwangeren met suikerziekte, overgewicht of chronische hypertensie vergeleken met een controle groep van gezonde zwangere vrouwen. Vrouwen met deze aandoeningen hebben namelijk een verhoogd risico op het ontwikkelen van preeclampsie. De exacte reden hiervan is niet duidelijk, maar gedacht wordt dat het maternale endotheel is aangetast.

De ARI van zwangeren met suikerziekte (zowel type 2 diabetes mellitus als diabetes gravidarum (zwangerschapssuiker)) of overgewicht bleek echter niet veranderd. Dit kan mogelijk verklaard worden door goede therapietrouw met goede glucosewaarden en de

relatief korte duur van de aandoening in deze onderzoeksgroep. Het is bekend dat vrouwen met een slechte suikerregulatie en complicaties daarvan juist het hoogste risico op preeclampsie hebben.

Vrouwen met chronische hypertensie bleken echter wel een significant lagere ARI te hebben dan de controlegroep van gezonde zwangeren met een normale bloeddruk (hoofdstuk 6). De ARI in deze vrouwen was vergelijkbaar met die van vrouwen met preeclampsie. Er bleek geen verschil tussen vrouwen met en zonder medicatie hiervoor, en het verschil bleef bestaan wanneer vrouwen die later gesuperponeerde preeclampsie ontwikkelden werden uitgesloten.

In hoofdstuk 6 en 8 werd onderzocht of met behulp van transcraniele Doppler en berekening van de autoregulatie te voorspellen is welke zwangere vrouwen later in de zwangerschap preeclampsie zullen ontwikkelen. Hoewel preeclampsie of het verergeren ervan niet te voorkomen is, kan het opsporen van een hoog-risico groep leiden tot vroege diagnostiek en behandeling, wat de uitkomst van moeder en kind kan verbeteren.

In hoofdstuk 6 is een tweede analyse uitgevoerd om vrouwen te vergelijken die na de meting wel of niet preeclampsie ontwikkelden. Van de vrouwen in de controlegroep ontwikkelden 3 (10%) preeclampsie, en de ARI van deze vrouwen was niet verschillend van de vrouwen die geen preeclampsie ontwikkelden. Hetzelfde geldt voor vrouwen met zwangerschapshypertensie.

De ARI van vrouwen met chronische hypertensie die later gesuperponeerde preeclampsie ontwikkelden was echter wel al verlaagd op het moment van de meting. Deze ARI was vergelijkbaar met zwangere vrouwen die al gesuperponeerde preeclampsie hadden. Dit kan op twee manieren worden uitgelegd.

Ten eerste is het mogelijk dat veranderingen in cerebrale autoregulatie ontstaan voordat er klinische symptomen van de ziekte zijn opgetreden. Deze theorie wordt ondersteund door het feit dat de autoregulatie bij mensen van middelbare leeftijd en langer bestaande chronische hypertensie niet verandert. Daarnaast wordt momenteel veel onderzoek opgedaan naar de bloedwaarden van zogenaamde angiogene factoren. Deze kunnen in sommige gevallen 5 tot 10 weken voor het ontstaan van preeclampsie reeds aangetoond worden.

Een tweede hypothese is dat de verlaagde ARI een indicatie is van al langere tijd bestaande endotheeldysfunctie, waardoor deze zwangeren gevoeliger zijn voor het ontwikkelen van gesuperponeerde preeclampsie. Dit wordt ondersteund door het feit dat vrouwen met chronische hypertensie preeclampsie ontwikkelen bij kleinere verstoringen van de angiogene factoren in het bloed.

In deze studie zijn maar kleine groepen geanalyseerd; nieuwe grotere studies zijn nodig om dit nader te onderzoeken.

In hoofdstuk 8 werd transcraniële Dopppler gebruikt om de voorspellende waarde van de pulsatility en resistance index (RI en PI) van de arteria cerebri media voor de ontwikkeling van preeclampsie te analyseren. De RI en PI in het tweede trimester van laag-risico zwangeren leek inderdaad de latere ontwikkeling van preeclampsie te voorspellen. Dit was in overeenstemming met eerdere studies, waarin een verlaagde PI en RI was gezien, mogelijk wijzend op een hyperdynamische circulatie met toegenomen hartminuutvolume en verlaagde perifere weerstand. De vrouwen in deze studie ontwikkelden allemaal een relatief milde en late vorm van preeclampsie.

Een algemene discussie en conclusie zijn beschreven in hoofdstuk 9. Uit dit proefschrift blijkt dat bij een gezonde zwangerschap er sprake is van redistributie van de bloeddoorstroming in de hersenen van de voorste hersenkwabben naar de achterste. Dit zou kunnen verklaren waarom vrouwen met preeclampsie met name klachten hebben die passen bij de functies van de achterkwab, zoals het gezichtsvermogen. Daarnaast leidt de zwangerschap tot een verbeterde cerebrale autoregulatie van de arteria cerebri media.

Verder werd geconcludeerd dat zwangeren met preeclampsie een verstoorde cerebrale autoregulatie hebben. Ditzelfde gold, in nog ernstigere mate, voor vrouwen met gesuperponeerde preeclampsie. Bij zwangere vrouwen met chronische hypertensie is er ook sprake van een verstoorde autoregulatie, en met name bij de vrouwen die later in de zwangerschap gesuperponeerde preeclampsie gaan ontwikkelen. Zwangeren met suikerziekte, overgewicht of zwangerschapshypertensie hebben daarentegen een autoregulatie welke vergelijkbaar is met gezonde zwangeren.

Naast de autoregulatie bleek ook de cerebrovasculaire reactie op het inhouden van de adem afwijkend bij vrouwen met preeclampsie. Dit kan mogelijk wijzen op een verstoorde sympathetische of myogene respons.

Tenslotte werd de mogelijke waarde van transcraniele Doppler voor het voorspellen van preeclampsie in een laag-risicogroep beschreven. Het proefschrift werd afgerond met enkele aanbevelingen voor toekomstig onderzoek.

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*If you're walking down the right path and you're willing to keep walking, eventually you'll make progress. (Barack Obama, 2008)*

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# ABOUT THE AUTHOR

Teelkien Roelfien van Veen was born on June 30, 1987 in Groningen, The Netherlands. She grew up with her older brother and twin sister in Haren, and later moved to Glimmen. After obtaining her high school diploma from the Willem Lodewijk Gymnasium in Groningen in 2005, she started medical school at the University of Groningen.

In 2008, after completing her Bachelors degree, she moved to Salt Lake City, Utah, for one year to start a research internship with prof. Belfort at St Mark's hospital, which subsequently led to admission to the MD/PhD program and funding to study the cerebral autoregulation in pregnancy. Between 2009 and 2015, she has worked on this thesis in Leicester, with prof. Panerai, in Houston, again with prof Belfort, in Austin with dr. Haeri, and in Groningen with prof. van den Berg and dr. Zeeman. In the meantime, she continued her medical education by training in the University Medical Center in Groningen and the Isala Clinics in Zwolle. She completed her final rotations at the department of Obstetrics and Gynaecology and the department of Internal Medicine in the Isala Clinics.

In the summer of 2014, Teelkien received her medical degree cum laude and started her clinical career in Obstetrics and Gynaecology at the Isala Clinics. In October 2015 she started working at the Isala Fertility Center.

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